DOES NOT CIRCULATE

UNIVERSITY OF MICHIGAN

Vol. 231, No. 3 MARCH, 1956 MAR 27 1956 No. 1007

HOSPITAL LIBRARY

# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

REG. U. S. PAT. OFF.
ESTABLISHED 1820

*Editor*
RICHARD A. KERN, M.D.

*Associate Editor*
THOMAS M. DURANT, M.D.

*Assistant Editor*
CHRIS J. D. ZARAFONETIS, M.D.

| | | | | |
|---|---|---|---|---|
| Carl Bachman | McKeen Cattell | Harry Gold | C. G. Johnston | C. Thorpe Ray |
| Herman Beerman | Frank R. Drake | John E. Gordon | John G. McAfee | Roger W. Reed |
| Wm. L. Benedict | G. Lyman Duff | David M. Gould | A. Harry Neffson | John H. Stokes |
| A. M. Bongiovanni | Franklin G. Ebaugh | Theodore H. Ingalls | Franklin L. Payne | H. P. Wagener |
| George E. Burch | Noah D. Fabricant | N. R. Ingraham, Jr. | I. S. Ravdin | Irving J. Wolman |

**Complications of Meningococcus Infection in a Series of Sixty-three Consecutive Sporadic Cases.** By JAMES L. TOBIN, COL., USAF, MC. 241

**Exfoliative Gastric Cytology.** By LEO VAN DER REIS, M. D., J. ALFRED RIDER, M.D., PH.D., and JOHN K. FROST, M.D. 249

**Epidemiological Aspects of Cases of Blastomycosis Admitted to Memphis, Tennessee, Hospitals During the Period 1922-1954: A Review of 86 Cases.** By ERNEST W. CHICK, M.D., WHEELAN D. SUTLIFF, M.D., JENNIE H. RAKICH, R.N., and MICHAEL L. FURCOLOW, M.D. 253

**Joint and Bone Diseases Due to Mycotic Infection.** By ELAM C. TOONE, JR., M.D., and JOHN KELLY, M.D. 263

**Further Observations on the Cardiovascular Effects of Sodium Lactate: Effect in Normal Subjects and in Various Arrhythmias.** By SAMUEL BELLET, M.D., FRED WASSERMAN, M.D., and JEROME I. BRODY, M. D. 274

**The Use of Iodipamide Methylglucamine (Cholografin High Potency) as a Contrast Medium for Intravenous Cholangiography.** By J. EDWARD BERK, M.D., SC.D., HARRY Z. MELLINS, M.D., and MARVIN BRODIE, M.D. 289

**The Effect of Pentolinium on Renal Hemodynamics and Water and Electrolyte Excretion: A Comparison with Hexamethonium.** By JOHN H. MOYER, M.D., and ROBERT L. HERSHBERGER, M.D. 294

**The Relation Between Appearance and Behavior of the Islands of Langerhans in Man.** By FRANCIS D. W. LUKENS, M.D., and W. WALLACE DYER, M.D. 313

**Progress of Medical Science**

**Pathology and Bacteriology—Recent Advances in the Laboratory Diagnosis of Tuberculosis.** By ROGER W. REED, M.A., M.D., C.M., and O. MORGANTE, M.D., M.Sc. 320

**Preventive Medicine and Epidemiology—Arctic Environment and Intestinal Infection.** By JOAN G. BABBOTT, M.D., FRANK L. BABBOTT, JR., M.D., and JOHN E. GORDON, M.D. 338

**Physiology—Proceedings of The Physiological Society of Philadelphia, November 15, 1955** 361

**Book Reviews and Notices** 365

Complete contents on adv. page 8

OWNERS AND PUBLISHERS LEA & FEBIGER PHILADELPHIA 6, PENNA.

Copyright, 1956, by Lea & Febiger. All Rights Reserved. Entered as second-class matter November 5, 1887 at the Post Office at Philadelphia, Pa. under the act of March 3, 1879

PUBLISHED MONTHLY. SUBSCRIPTIONS, TEN DOLLARS A YEAR

# When Blood Pressure Soars to Dangerous Heights

You can depend on Hepvisc to reduce readings to safer levels, as well as to bring your patients gratifying relief from the subjective symptoms.

**AVERAGE BLOOD PRESSURE BY AGE** (Auscultatory Method)

| AGE | Under 18 | 18-22 | 23-27 | 28-32 | 33-37 | 38-42 | 43-47 | 48-52 | 53-57 | 58-62 | 63 + |
|---|---|---|---|---|---|---|---|---|---|---|---|
| SYSTOLIC Male | 117.0 | 120.2 | 121.2 | 121.8 | 122.9 | 124.3 | 126.0 | 128.1 | 130.3 | 131.9 | 134.2 |
| Female | 114.7 | 116.4 | 117.7 | 118.7 | 120.4 | 123.6 | 127.1 | 129.8 | 132.5 | 133.7 | 135.4 |
| DIASTOLIC **Male | 76.4 | 78.1 | 78.8 | 79.5 | 80.4 | 81.4 | 82.3 | 83.3 | 84.3 | 84.5 | 84.0 |
| Female | 75.8 | 77.1 | 78.0 | 78.6 | 79.9 | 81.9 | 83.9 | 85.4 | 86.8 | 86.8 | 84.4 |

**Fourth phase
*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

## ···HEPVISC REG. U. S. PAT. OFF.

**Hexanitrate of Mannitol + Viscum Album**

*Available in Bottles of 50-500-1000 tablets.*

*Complete Literature and Professional Samples Sent upon Request*

**THE ANGLO-FRENCH DRUG CO. (U.S.A.) LTD.**

**75 Varick St., New York 13, N. Y.**

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

MARCH, 1956

## ORIGINAL ARTICLES

# COMPLICATIONS OF MENINGOCOCCUS INFECTION IN A SERIES OF SIXTY-THREE CONSECUTIVE SPORADIC CASES

By James L. Tobin, Col., USAF, MC

(From the Medical Service, 3650th USAF Hospital, Sampson Air Force Base, New York)

In these days of antibiotics and antimicrobials, infectious diseases have dropped in incidence and severity. One senses the attitude that they are considered negligible: a few shots or capsules and the patient is well. For one who works in a hospital where pneumonia and meningitis are seen often, infectious diseases are by no means entirely curable or lacking in perplexing complications. Due to individual variation of patient or organisms, antibiotics sometimes fail, or at least do not prevent all sequelae. Or, to take a more optimistic view, one might say that people live today to have complications from which death spared them in the past.

During a 4-year period at an Air Force recruit training base with a constantly changing population of 15,000 recruits on the average, 63 sporadic cases of meningococcic meningitis occurred. Although there was a seasonal incidence (most of the cases occurred in March or April), new cases were seen in every month of the year. There was never an instance of 2 cases occurring in the same flight (a group of 72 men who work together and live in the same barracks), presumably because, as a preventive measure, 2 gm. of sulfadiazine were given to each member of the flight in which a case of meningitis developed as soon as the diagnosis was made.

The combination of sulfadiazine and penicillin was used for no particular reason except that we started out that way and continued with it to be consistent. Sulfadiazine is certainly adequate. Penicillin has been used with success alone. However, several cases of meningitis have appeared in individuals who have just finished courses of penicillin for one reason or another, and probably still had a measurable level in the blood stream.

One man came down with meningitis 2 days after the end of a 10-day course of oral penicillin given as prophylaxis against the streptococcus prevailing here. Another airman developed meningitis seven days after a 900,000 unit injection of Bicillin which usually gives a recognizable blood level for 3 weeks. This indicates that a much higher blood level of penicillin is necessary to prevent or treat meningitis.

In many of these patients the urine was grossly bloody after large doses of sulfadiazine. As they were severely ill

with meningitis, the drug was continued. None developed a lower nephron nephrosis.

The disease occurred under conditions allowing early discovery and treatment was begun at once. Some even began under our noses, as it were, when the airmen were in the hospital for another reason. In spite of early and what is usually considered adequate treatment, there were a large number of complications. Not all the complications were severe or permanent, but enough were to prove that the meningococcus is not rendered entirely harmless by antibiotic treatment.

TABLE 1.—COMPLICATIONS OCCURRING IN 63 CASES OF MENINGOCOCCUS INFECTION

| | | % |
|---|---|---|
| Total cases in series | 63 | 100 |
| Cases with complications | 32 | 50.8 |
| Deaths | 6 | 9.8 |
| Waterhouse-Friderichsen syndrome | 9 | 14.3 |
| Nerve involvement | | 27 |
| Eye muscle paresis | 6 | |
| Hearing loss | 6 | |
| Herpes zoster | 2 | |
| Sensory loss | 1 | |
| Facial paralysis | 2 | |
| Pulmonary edema | 1 | 1.6 |
| Nephritis and pneumonia | 1 | 1.6 |
| Gastrointestinal hemorrhage | 2 | 3.2 |
| Skin involvement | | |
| Erythema nodosum | 1 | 14.2 |
| Ulceration | 7 | |
| Stevens-Johnson syndrome | 1 | |
| Electrocardiographic changes | 6 | 9.5 |

Meningitis was a scourge during World War I. Although not epidemic in World War II, it was responsible for a number of deaths. Moritz and Zamcheck[13] in a review of about 1000 cases of sudden and unexpected death in young soldiers indicate 352 died of meningococcus meningitis. Of these 110 died within 12 hours and 60 within 6 hours after coming under medical observation. The younger the man, the shorter was the course in fatal cases.

Many complications of meningitis are described in the literature: Waterhouse-Friderichsen syndrome[8,18], the cutaneous lesions[9], gangrene of extremities following large vessel thrombosis[5,16], myocarditis[10], endocarditis[11], pericarditis[4], purulent arthritis[3], osteoperiostitis[2], glycosuria and a transitory diabetic syndrome[6,17], paraplegia[12], mental deficiency, deafness, strabismus, and nystagmus[14], bilateral subdural hematoma[1], causalgia,[19], mental symptoms[15], personality changes[7], and massive gastrointestinal hemorrhage[7].

All the varieties of complications which arose in the patients in this series have been seen before, even though some are uncommon. They are presented here chiefly to call attention to the frequency of their occurrence in sporadic cases and to show that they happened in spite of early intense treatment. Perhaps it was because these cases were sporadic, that so many complications developed. The organism, which is a frequent inhabitant of the human throat, finally found an individual who was a new and fertile culture medium. By being able to develop unhindered in this susceptible person, it created more damage.

Table 1 lists the type and number

of complications which outnumber the actual cases because several sometimes occurred in the same patient.

The most serious complication was, of course, the Waterhouse-Friderichsen syndrome which accounted for 4 of the 6 deaths in the series. The patients with other complications for the most part tended to recover during the period of observation here. Some complications left permanent damage which was not incapacitating and the men were allowed to return to duty.

If one does not make death part of the criteria for Waterhouse-Friderichsen syndrome, there were 9 cases which showed its outstanding findings of extensive coalescing petechiae, ecchymotic areas, and peripheral vascular collapse. Most of these patients arrived at the hospital in shock. A variety of supportive measures were used. We expected the best results from cortisone, but there was nothing spectacular about it. Continuous intravenous norepinephrine usually raised the blood pressure, but did not necessarily sustain it. Perhaps the assault to the adrenal had already been accomplished with such damage that the rate of absorption of even intramuscular cortisone could not mend it. For this reason, we expected more from an intravenous preparation. However, one of the patients in whom this medication was used at the time the blood pressure took a sudden drop, failed to recover. Apparently, when the blood pressure falls it is already too late. At present, we are using intravenous cortisone on all cases as soon as they are diagnosed, with the hope the blood pressure will remain above shock levels. In the young people we deal with, the risk seems small and we may gain something.

To perpetuate the Irish bull, one might say these patients would get well if only they lived long enough. Any supportive measure that can keep the patient alive until the sulfadiazine can subdue the infection seems justified. In each of three of the Waterhouse-Friderichsen syndrome deaths, there was a necropsy with the finding of extensive bilateral adrenal hemorrhage. The fourth, which was clinically identical, showed congestion of the adrenals, but no frank hemorrhage at all, an indication that functional damage is done early in the disease, before the breakdown of the walls of the cortical sinuses occurs.

**Case Reports: Waterhouse-Friderichsen Syndrome.** CASE 1. *F.T. (Record number 15656):* After two days of malaise, this man came to sick call because of severe backache. When he arrived at the hospital, he was conscious, showed widespread petechiae, and a blood pressure of 75/60 mm. Hg. Treatment was begun at once with sulfadiazine and penicillin. During the first 72 hours, his blood pressure varied from 90/60 to 50/30. Efforts to maintain it above shock levels consisted in giving serum albumin intravenously and administering DOCA. Because of his low urine output on the second day, sulfadiazine was discontinued and he was treated with penicillin alone.

On the fourth day, his electrocardiogram showed signs of hypopotassemia, and potassium chloride was administered orally.

On the third day, he developed a painful swollen right knee joint but this rapidly cleared by the fifth day.

Many of the petechiae coalesced and eventually sloughed, forming deep ulcerations which healed slowly.

He developed a subacute bacterial endocarditis due to S. *alkaligenes fecalis* while convalescing from his meningitis on the tenth day. This in itself is not considered a complication of meningitis except that the lowered resistance of the patient allowed him to get a second infection easily.

This patient recovered and returned to duty after 67 days hospitalization.

CASE 2. *E.E. (Record number 17728):* This patient became ill with abdominal pain, fever and vomiting. He had no headache or backache. When first examined, he had a temperature of 100° F., scattered petechiae, no nuchal rigidity, and a blood pressure of 80/60. He was begun at once on treatment with 5 gm. of sodium sulfadiazine intravenously and 250,000 units of penicillin every 3

hours. During the next 6 hours, there was a rapid spread of the petechiae. At the ninth hour, the blood pressure fell suddenly. He improved somewhat on treatment with 400 mg. of cortisone orally, 5 mg. of DOCA, and 1000 ml. of whole blood. However, he showed a gradual fall in blood pressure which responded very little to further treatment, and he died about 24 hours after admission.

A necropsy showed marked congestion of the adrenals with no frank hemorrhage. There were diffuse petechial hemorrhages throughout the viscera.

CASE 3. *B.T. (Record number 22319):* This patient entered the hospital because of pharyngitis, malaise, and nausea. After 24 hours of not appearing too ill, he suddenly developed severe generalized petechiae, mottled cyanotic skin, and his blood pressure fell to 50/0. He was given the usual intravenous sodium sulfadiazine, penicillin, plus 300 mg. of cortisone intramuscularly. There was a 6-hour period in the first 24 hours during which the blood pressure was unobtainable.

On the second day, his blood pressure rose to 90/60 but fell again on two occasions. Each of these second declines seemed to be relieved by giving serum albumin intravenously.

Because he demonstrated electrocardiographic changes indicating myocarditis and recovered slowly, he was retained in the hospital. On the 30th day of hospitalization, he developed a severe Stevens-Johnson syndrome which consisted of bullous erythema multiforme with oral, rectal, urethral and conjunctival involvement. Most of the skin of his back became one big blister and exfoliated. This episode was not considered so much a complication of meningitis as a complication of the treatment. There have been a number of instances of bullous erythema multiforme here which appeared related to the taking of penicillin and sulfadiazine.

This airman recovered after 131 days of hospitalization.

CASE 4. *D.P. (Record number 22635):* This patient developed a sudden chill, followed by a temperature of 105.6° F. while he was a patient in the hospital because of a cold. Petechiae rapidly developed and coalesced, forming large ecchymotic areas. His blood pressure remained near 90/50 the first 24 hours, but the patient was unconscious and in poor condition. The blood pressure fell to 50/30 for several hours on the second day. On the third day, the blood pressure had risen to 100/60 and subsequently remained at this relatively normal level.

He was treated with the usual sulfadiazine and penicillin. When his blood pressure fell, serum albumin was administered with good response.

In the areas of ecchymosis, sloughing began on the tenth day. A large area over the left elbow, over the sacrum, and most of the lateral aspect of the right thigh sloughed away. This required an extended period of skin grafting and the patient remained in the hospital for 234 days.

CASE 5. *J.Y. (Record number 31465):* After a day of malaise, chill, cough, and weakness, this patient developed an extensive petechial rash. He appeared in shock and critically ill. Treatment to restrain his falling blood pressure was begun at once with serum albumin and adrenalin in oil. His blood pressure remained at 68/50. Intravenous sulfadiazine and penicillin were given and by the next day, he was greatly improved with the blood pressure 100/70.

CASE 6. *A.D. (Record number 32745):* This patient had 2 days of malaise before he developed a sudden chill and collapse. When first examined, his temperature was 105° F., he was in an agitated stupor, his blood pressure was 94/30, and there were many petechiae. On the second day his blood pressure dropped but responded to 250 ml. of plasma, adrenalin in oil, and finally maintained on norepinephrine by intravenous drip at about 90/30.

The petechiae spread rapidly, coalesced, and many ecchymotic areas developed. By the fourth day, dry gangrene of the finger tips developed with gangrene of the terminal phalanx of the right index finger and left little finger.

By the third day, his general condition was good, and his blood pressure was 120/70. However, on the seventh day, he was restless, pale, and had a rapid pulse. It was evident that there was internal bleeding. Fifteen hundred milliliters of blood were given but he died about 6 hours after the signs of hemorrhage were discovered.

At necropsy, there was severe adrenal hemorrhage bilaterally. His stomach and bowel were filled with blood. The only site of bleeding appeared to be several superficial erosions in the prepyloric area of the stomach.

CASE 7. *J.M. (Record number 39899):* This man had had a cold for a week. Suddenly, he had a chill and became unconscious. When brought to the hospital, his temperature was 105° F., he was stuporous, and had a gener-

alized petechial rash. On admission, his blood pressure was 70/40 but fell to 50/0 in the first hour. He was given intravenous sulfadiazine, penicillin, norepinephrine and serum albumin simultaneously, and responded with a very gradual rise in blood pressure. By the third day, his blood pressure was back to 100/60 and he continued to do well.

CASE 8. *G.H. (Record number 57787):* This patient complained of sudden headache, fever, and was comatose when he arrived at this hospital. At the dispensary, he had no petechiae, but by the time he arrived at the hospital half an hour later, there was an extensive rash. His blood pressure, which was 110/68 on entry, fell to 60/40 in the first two hours. He was treated vigorously with sulfadiazine intravenously, norepinephrine, 100 mg. of cortisone intramuscularly, 40 mg. of ACTH, adrenalin, and Coramine but showed no response and died 4 hours from the onset of illness.

At necropsy, there was severe bilateral adrenal hemorrhage with many petechiae over the viscera. There was no meningitis grossly or microscopically.

CASE 9. *R.T. (Record number 63407):* This man had a sudden onset with a chill, fever, backache, nausea, and vomiting. When he arrived at the hospital, his temperature was 105° F., he was in a restless stupor and had few petechiae. Out of this group of nine, he was the only one with a stiff neck. He was treated with sulfadiazine, penicillin, intramuscular cortisone, norepinephrine drip, and serum albumin. There was a very rapid spread of his petechial rash after the second hour in the hospital. His blood pressure on admission was 78/54 but treatment seemed to help in raising it to 100/50. However, it fell again in spite of these measures after the twelth hour. The patient died about 24 hours after the onset.

Necropsy showed severe bilateral adrenal hemorrhage, generalized petechiae in the viscera, and early meningitis.

**Meningitis and Acute Nephritis.** CASE 10. *H.J. (Record number 78389):* This man, who had been known to have an elevated blood pressure for 2 years, spent a week in the hospital because of a sore throat. He felt well the day after he left the hospital, but the following day he awakened with edema of the face and ankles and passed red urine. He was brought directly to the hospital from his barracks because he looked so acutely ill. When first seen, he was lethargic, had edema of the face and ankles, his temperature was 101° F., but he also had a petechial rash and a stiff neck. The spinal tap showed cells and a positive culture for meningococcus was obtained later. He was begun on penicillin, one million units, every 2 hours. Four grams of Gantrisin were given with the belief that it would be less likely to damage the kidney. His urinary output was low so no more was given. On admission, the blood pressure was 150/100, but it fell to 118/60 by the third hour.

He was given 100 mg. of Cortef IV every 8 hours. On the third day, he passed a copious tarry stool. His chest seemed to fill with fluid and he was digitalized with Cedilanid. His course was steadily downhill and he died 3 days after the onset.

In view of his known hypertension for 2 years, one can speculate that he may have had a chronic nephritis, reactivated because of his streptococcus infection. This left him vulnerable to any virulent organism which in this case was the meningococcus.

**Gastrointestinal Hemorrhage.** There were 2 cases in this series in which there was severe gastrointestinal hemorrhage. In the case of A.A. (record number 32745), it occurred on the seventh day and was the immediate cause of death. The site of bleeding was superficial ulceration in the prepyloric region of the stomach. In the case of J.H. (record number 18681), it occurred at the end of the second day and was manifested by the passage of a copious tarry stool. At necropsy, no particular source of bleeding was discovered.

**Meningitis and Pulmonary Edema.** The one case in which this complication occurred illustrates the difficulty of making any estimate of the prognosis early in the disease. Two airmen with meningitis entered the hospital the same evening. One was unconscious and critically ill; the second conscious, in good condition, able to give a history, and take oral medication. This man apparently slept during the night, his blood pressure did not fall, but shortly after awakening in the morning, he developed a rapid heart rate, dyspnea, began to cough up pinkish froth, and soon died of acute pulmonary edema. At necropsy, he showed

cardiac dilatation, pulmonary congestion and edema, hydrothorax bilaterally, petechiae, hemorrhages of the skin and viscera. The adrenal on the right side was normal and on the left showed a small area of hemorrhage involving about 10% of the gland.

The man who entered the hospital critically ill responded to treatment and recovered without sequelae.

The mechanism of pulmonary edema in meningitis is not explained. It is mentioned as the cause of death in a number of cases reported in the Moritz and Zamcheck series[13]. The heart muscle did not look especially abnormal microscopically in this airman, but it may be that the overpowering infection caused a toxic myocarditis resulting in sudden failure before cellular changes could be seen.

**Facial Paresis.** Unilateral partial paralysis of the face occurred twice (record number 5733, T.F. and record number 15619, H.C.). Both began about the eleventh day of illness and consisted of being unable to close the eye, smile, whistle, or wrinkle the forehead on the affected side. Both men improved while in the hospital; however, although they could both close their eyes when discharged to duty, there was still a noticeable weakness present in the facial muscles. T.F. also had a persistent nerve type deafness above 1024 cps in the right ear.

**Neuritis.** CASE 11. *I.T. (Record number 60683):* On the fourth day of illness complained of numbness and weakness of the left leg. The weakness cleared by the seventh day but there was a broad area of loss of sensation to pin-prick in the lower two-thirds of the anterolateral surface of the left thigh approximating the L2 segment. The size of the area gradually shrank, but by the time of his discharge on the 25th day, a 4 by 5 inch area of diminished sensation remained on the lateral surface of the left thigh a few inches above the knee.

**Herpes Zoster.** CASE 12. *L.H. (Record number 22353):* On the second day of illness, this airman developed herpes simplex on the lips and roof of the mouth; on the fifth day, herpes zoster on the left side of the neck; on the sixth day, painful herpetic lesions on the palmar surface of the right thumb, especially in the pulpy area of the distal end. The lesions had cleared by the 23rd day. This man also had deafness.

CASE 13. *J.H. (Record number 68846):* On the third day of illness, herpes appeared on the right upper lid and conjunctiva over the distribution of the supraorbital nerve. Although the inner surface of the upper lid was involved and later the lower lid, there was no involvement of the cornea. The man had a very painful and inflamed looking eye, but the lesions gradually cleared by the 19th day. He also had III and IV cranial nerve involvement.

**Eye Muscle Weakness.** Of the 6 patients in whom the eye muscles were involved, only two suffered permanent damage and in one of these it was slight. Most of the difficulty with eye movements began on the first or second day. One man had diplopia on gazing to the left which lasted 5 days. One had persistent nystagmus brought on by looking to the left. The trouble began on the sixth day and cleared up on the eleventh. One had weakness of the medial rectus bilaterally which improved by the fifth day and was entirely gone by the 20th day. A second case of nystagmus, beginning on the second day, cleared on the fourth day.

CASE 14. *J.L. (Record number 40001):* This man, on the second day of illness, developed a marked strabismus which was apparently permanent. A review of his original physical examinations and questioning the parents and the man gave no evidence of previous strabismus. The mechanism was bilateral weakness of the lateral recti with overaction of the internal oblique muscles.

CASE 15. *J.H. (Record number 68846):* This patient is of interest because 2 days before he felt ill otherwise, he developed a sudden spell of transient blindness which lasted a few minutes and was followed by diplopia. He then went on to develop meningitis and herpes zoster in the region of the right eye. His diplopia improved by the 19th hospital day and on discharge, the eye movements

appeared normal but there was a permanently weak convergence.

**Hearing Loss.** There were 8 patients who complained of hearing loss or were noticed to be hard of hearing during their illness. Unfortunately, there were no audiograms taken before the meningitis began, and there was often some delay in getting an audiogram after the complaint was noted. The deafness in 6 cases was noted about the fourth day. In two, it was noticed on the 12th day.

Two showed no abnormality by the time the audiogram was taken, although the patient and ward personnel felt deafness existed during part of the illness.

Two showed conduction type loss of 40 decibels which may have existed before the illness.

Four showed a persistent nerve type deafness. Two of these were losses above the speech range. One had a 40 decibel loss in the speech range; he showed some improvement, and though still deaf was able to return to duty. The fourth had most of the loss in the left ear and was able to do duty.

**Skin Complications.** All the patients with extensive rashes are likely to develop superficial gangrenous areas which break down into ulcers. The greatest difficulty occurs in those with Waterhouse-Friderichsen syndrome. Of the 9 cases with skin complications, five were associated with this syndrome. D.P. (Record number 22635) with large sloughing areas, was previously described (Case 4) as was A.D. (Record number 32745) (Case 6) who developed gangrene of the finger tips.

CASE 16. *J.Y. (Record number 31465)* had numerous small ecchymotic areas which broke down and resulted in deep ulcerations which were slow to heal and did not clear completely until the sixth week of illness.

CASE 17. *F.G. (Record number 15656)* had ulcers which were deep and slow healing.

CASE 18. *B.T. (Record number 22319)* developed Stevens-Johnson syndrome 30 days after his meningitis which was very severe and took 30 days to clear up.

CASE 19. *R.K. (Record number 76600)*, whose meningitis appeared to run an uncomplicated course, was retained in the hospital 30 days because of deep ulcerations ½ to 1 inch in diameter.

There were 2 patients in violently delirious condition who were required to have ankle restraints in addition to special corpsmen to keep them in bed. Although the restraints were fleece-lined and applied less than 24 hours, ulcerations developed in ecchymotic areas under the restraints, especially over the tendon of Achilles. These patients recovered from meningitis promptly, but they were unable to wear shoes and could not be discharged until the 70th day.

CASE 20. *N.S. (Record number 30432)* complained of scattered red 1 to 2 cm. painful lesions on the extensor surfaces of his legs and arms, as well as stiffness of the joints. He had a temperature of 101° F. By the second day, the nodules appeared on his feet and abdomen also. The initial diagnosis was acute rheumatic fever with erythema nodosum, but on the third day, the nodular lesions grew less and a few petechiae appeared. A blood culture was positive for the meningococcus. When the petechiae appeared, he was treated with sulfadiazine immediately after blood cultures were done, and he promptly got well without developing meningitis.

**Electrocardiographic Changes.** In any severe toxic state, one might well expect electrocardiographic changes. Only six of importance were noted in this series, but few were taken during the busy early days of the illness. A total of 12 cases were examined in this way. Four were normal. Two had incomplete right bundle branch block, a near insignificant thing.

CASE 21. *E.V. (Record number 73025)* on the first day of illness had a wandering pacemaker but was normal on the fourth day.

CASE 22. *F.C. (Record number 36185)* on the first day had low to isoelectric T waves in leads 2, 3, $aV_F$, $V_{4,5 \text{ and } 6}$. The next tracing taken a week later was normal.

CASE 23. *A.M. (Record number 15513)* on the first day of illness had a constant trigeminal rhythm due to regular premature ventricular contractions. One month later, he showed only occasional ventricular premature contractions.

CASE 24. *B.T. (Record number 22319)* had severe meningitis of the Waterhouse-Friderichsen type. On the fourth day of illness, he showed a 1-mm. ST elevation in Leads 2 and 3. The T waves were diphasic and low in $aV_F$; inverted in $V_{1,2,3}$; isoelectric in $V_4$. The patient recovered rather slowly and was still in bed after 30 days when he developed Stevens-Johnson syndrome. The electrocardiographic findings were of the same sort but improved and grew worse during this period and slowly returned to normal after 60 days in the hospital.

CASE 25. *F.T. (Record number 15656)* on the fourth day of illness showed low voltage QRS complexes with a prolonged QT interval. $T_{1,2,3}$; $V_{4,5,6}$ were low sloping and slurred. This was interpreted as being due to hypopotassemia but little change occurred after oral administration of potassium chloride. On the 10th hospital day his electrocardiogram showed $ST_3$, $V_{2,3 \text{ and } 4}$ depressed; $T_{1,2,3}$, $V_{2,3,4}$, diphasic; $T_{5 \text{ and } 6}$ negative.

This man developed subacute bacterial endocarditis on the 10th day of illness when his meningitis seemed to be clearing nicely. The abnormal electrocardiogram persisted with gradual improvement until a normal tracing was found on the 49th day.

CASE 26. *J.H. (Record number 68846)*, on the fourth day of illness showed 1-mm. ST elevation L2, 3; $T_3$ diphasic; $TaV_F$ low; $TV_{1,2,3}$ inverted; $TV_4$ isoelectric. On the eighth day the ST elevation was the same; $T_3$ was diphasic, $aV_F$ normal; $TV_1$ inverted. The tracing was normal on the 12th day.

**Summary.** A report is made of 63 consecutive sporadic cases of meningococcus infections in Air Force recruits which occurred over a period of 4 years. These patients showed a high incidence of complications. There were 6 deaths in this series, 4 of which were due to Waterhouse-Friderichsen syndrome. Intramuscular cortisone did not seem to help greatly in the treatment. Norepinephrine was of more immediate aid. The possibility that intravenous cortisone given early might be of value was mentioned. Although the men were treated promptly with both sulfadiazine and penicillin, 50% of the cases had one or more complications.

REFERENCES

1. **Bernstein, P.:** New England J. Med., **230,** 482, 1944.
2. **Box, C. R., and Nickolson, T. G.:** Lancet, **1,** 239, 1917.
3. **Brown, M. G., and Gottduner, E. E.:** Mil. Surg., **94,** 270, 1944.
4. **Cattell, J. P.:** New England J. Med., **229,** 49, 1943.
5. **Defuccio, C. P., and Dresner, E. E.:** Pediatrics, **3,** 837, 1947.
6. **Fox, M. J., Kuzma, J. F., and Washam, W. T.:** A.M.A. Arch. Int. Med., **79,** 614, 1947.
7. **Gray, I., and Talisman, M. R.:** New York State J. Med., **47,** 1389, 1947.
8. **Hill, W. R., and Kinney, T. D.:** J. Am. Med. Assn., **134,** 513, 1947.
9. **Levin, A., and McElroy, D. M.:** Brit. J. Surg., **31,** 240, 1944.
10. **Logan, W. R.:** Edinburgh Med. J., **52,** 49, 1945.
11. **Lowe, C. V., and Diamond, L. K.:** A.M.A. Am. J. Dis. Child., **75,** 660, 1948.
12. **Mathews, J. D.:** Lancet, **2,** 149, 1949.
13. **Moritz, A. R., and Zamcheck, N.:** A.M.A. Arch. Path., **42,** 459, 1946.
14. **Nelson, J., Clyne, R. M., and Sharrott, J.:** Ann. Int. Med., **25,** 862, 1946.
15. **Pai, M. N.:** Brit. Med. J., **1,** 289, 1945.
16. **Saphir, O.:** Am. J. Path., **12,** 677, 1936.
17. **Stewart, M. M.:** Brit. Med. J., **2,** 319, 1945.
18. **Waterhouse, R.:** Lancet, **1,** 577, 1911.
19. **Weir, T. W. H., and Vantier, C. K.:** Brit. Med. J., **1,** 179, 1942.

*(Interlingua on page 288)*

# EXFOLIATIVE GASTRIC CYTOLOGY

By Leo van der Reis, M.D.
RESEARCH FELLOW IN MEDICINE

J. Alfred Rider, M.D., Ph.D.
ASSISTANT PROFESSOR OF MEDICINE

AND

John K. Frost, M.D.
INSTRUCTOR IN PATHOLOGY

(From the Departments of Medicine and Pathology and the Cancer Research Institute, University of California School of Medicine, San Francisco, California)

The cytologic examination of exfoliated cells has become established as a valuable adjunct in the detection, diagnosis and confirmation of neoplasms. It has been particularly successful in revealing lesions of the cervix and the bronchi[2,3,7]. As the technique has improved, the procedure has been applied with increasing accuracy to the detection of malignancies of the gastrointestinal tract[1,5,11-15]. The greatest degree of accuracy has been achieved in the detection of neoplasms of the stomach, but cytologic study of exfoliated material from the esophagus, rectum, colon and duodenum is often rewarding. In addition, examination of washings from the stomach may at times provide clues pointing to the presence of other conditions, such as pernicious anemia[6], atrophic gastritis and hypertrophic gastritis.

The purpose of the present study was to evaluate the diagnostic value of routine cytologic methods in patients suspected of having malignancies of the stomach and to detect any advantage existing between the use of the two mucolytic enzymes, papain and chymotrypsin. In this study only procedures routinely performed in the laboratory were utilized.

I. Chymotrypsin[11*]

a. *Buffer solution*

| | | |
|---|---|---|
| Sodium acetate | 13.6 gm. | Approximate pH 5.6 (Will stock indefinitely) |
| Glacial acetic acid | 0.6 ml. | |
| Aqua dist. | 1 liter | |

b. *Chymotrypsin*

One 7 mg. capsule dissolved in 500 ml. of the buffer solution (immediately before use).

II. Papain[9]

a. *Buffer solution*

| | | |
|---|---|---|
| Dibasic sodium acid phosphate | 350 gm. | Approximate pH 7.3 (Will stock indefinitely) |
| Normal hydrochloric acid | 400 ml. | |
| Aqua dist. | 5 gals. | |

b. *Papain*

Three level teaspoonfuls dissolved in 500 ml. of the buffer solution. (Can be stocked 24 hours if refrigerated.)

c. *Cystein*

One-half teaspoonful dissolved in papain-buffer solution (immediately before use).

*The chymotrypsin was made available by the Armour Laboratories, Chicago, Illinois.

**Methods.** A. SUBJECTS. The series consisted of 70 patients from the Gastrointestinal Clinic seen during the period of 7½ months covered by this study. They were consecutive and unselected, except for the presence of radiologic or gastroscopic evidence or symptoms indicative of gastric malignancy. Each patient underwent routine mucolytic enzymatic gastric lavage on one or more occasions.

B. MATERIALS. The solutions used for lavage contained either chymotrypsin or papain as the mucolytic enzyme.

C. TECHNIQUE. The specimen for examination is collected in the morning. The patient is given a small semi-liquid supper the night before, and nothing is taken orally before the examination. Very occasionally, if gastric retention is marked or if a previous examination was unsatisfactory due to retention, overnight Wangensteen suction is employed. A gastric tube is passed through the mouth to eliminate contamination with nasal cells and mucus, and the stomach is completely emptied by aspiration with a syringe. Five hundred milliliters of the buffer solution containing either papain or chymotrypsin is placed into the stomach. To lavage the entire mucosal surface, the recumbent patient rolls over several times during a period of 10 minutes. The solution is then aspirated. Maximum recovery of the solution is obtained by having the patient alternately lie on his left side and sit upright during the aspiration.

Ideally, in order to keep to a minimum the digestive action of the enzyme upon the exfoliated cells, the solution should be immediately centrifuged, smeared on glass slides and fixed at the bedside. At present, however, the specimens are transmitted to a separate laboratory for processing, and the actual elapsed time between collection and fixation approximates 25 minutes. The collection flasks containing the aspirates are usually packed in ice during this period to retard the digestive action. After the specimen is centrifuged at 2000 rpm for 10 to 20 minutes, the precipitated sediment is smeared upon glass slides, fixed immediately in an ether-alcohol solution (equal parts) and stained by a slight modification of the Papanicolaou method[8].

**Results.** During the 7½-month period covered by this study, a total of 84 gastric washings from 70 consecutive patients were examined cytologically. Four additional washings, which were unsatisfactory for objective technical reasons, are not included in this tabulation.

GROUP I. Five specimens from 4 patients contained cells which were reported as having been shed from a carcinoma. All 4 patients were subsequently proved to have adenocarcinoma of the stomach. In one of these cases, preoperative gastroscopic biopsies obtained under visualization revealed only hypertrophic gastritis. No evidence of local or lymph node metastases was found at the time of subsequent operation.

GROUP II. Thirteen gastric washings from 9 patients contained cells which were reported as inconclusive. Three of these patients were subsequently shown to harbor a malignancy of the stomach. One of these 3 patients was diagnosed cytologically by another lavage, and therefore is also included in Group I; the second patient was found at surgery to have adenocarcinoma of the stomach; the third, lymphosarcoma involving the gastric wall. Five of the remaining 6 patients had hypertrophic gastritis, one with a benign gastric ulcer confirmed at the time of operation; the sixth had a polyp of the stomach. None of these 6 patients had shown any evidence of malignancy during a follow-up period of from 5 to 12 months.

GROUP III. Sixty-six washings from 58 patients were reported to contain no malignant cells. Three of these patients were proved to have carcinoma. In one of these 3, a malignancy of the stomach had been demonstrated by a previous gastric lavage (see Group I); in the other 2 cases, the diagnosis of cancer was not made, although 5 gastric washings were examined. The remaining 55 patients (60 washings) have shown no evidence of malignancy during a follow-up period ranging from 5 to 12 months.

When an unequivocal cytologic diag-

nosis of malignancy was rendered, therefore, the accuracy in this study was 100% (Table1). When cells were present which were felt to be diagnostically inconclusive, 25% proved to harbor a cancer. When a negative report was rendered, 3% had carcinoma.

**Discussion.** In this series of 70 consecutive patients on whom mucolytic enzyme gastric lavage was performed for symptoms referable to the upper gastrointestinal tract, 8 were proved histologically to have a malignancy of the stomach. In 4 of the 8 patients, the gastric washings were diagnosed unequivocally as containing exfoliated malignant cells. Other established procedures had failed to diagnose cancer in one of these 4. In 2 of the remaining 4 cases, the appearance of the cells was diagnostically inconclusive, and the patients were proved by other methods to have cancer, one an adenocarcinoma and one a lymphosarcoma. In 2 cases no malignant cells were found, although the patients had proved adenocarcinoma. No false positive results were obtained.

TABLE 1.—CORRELATION OF CYTOLOGIC DIAGNOSES

| *Diagnosis Rendered* | *Proved Cancer* | *No Evidence of Cancer* | *Total Patients* |
|---|---|---|---|
| Positive | 4 (100%) | 0 (0%) | 4 |
| Inconclusive | 2 (25%) | 6 (75%) | 8 |
| Negative | 2 (3%) | 56 (97%) | 58 |
| | | | 70 |

The value and accuracy of this method depend mainly upon the technique employed in obtaining and preparing the sample, the thoroughness of the screening procedure, and the experience of the pathologist who interprets the microscopic specimen.

Reports by other investigators[4,10] indicate that of the two mucolytic enzymes used in our series, chymotrypsin yields better results. The relatively small size of this group of patients does not permit a true evaluation of the relative advantages of the two mucolytic enzymes. Nonetheless, certain advantages offered by chymotrypsin have become apparent during this study. In this group of patients, the diagnostic results yielded by both enzymes were essentially the same. Chymotrypsin lacks the sickening smell and taste of papain, making the procedure more acceptable to the patient. The preparation of the enzyme-containing solution is somewhat less complicated in the case of chymotrypsin. Furthermore, the amount of background debris in the stained chymotrypsin specimen has tended to be somewhat less.

There are many factors not utilized fully in this group of patients, which if employed would improve results. The utilization of a centrifuge at the site of aspiration would allow for immediate centrifugation, smearing and fixation, with better cellular preservation. In addition, centrifugation at 4000 to 5000 rpm for a much shorter period of time would give better cellular preservation and therefore better results. Ideally, a patient with retention in the fasting aspirate should be rescheduled and properly prepared. In this study the procedure was continued even in the presence of retention. Smears were not called unsatisfactory by the pathologist unless all cells were poorly preserved, as evidenced by the low rejection rate of 4 of 88 washings. Gastric lavage should not be performed after gastroscopy if silicone anti-foam agents are utilized, since they have been

found to cause rapid disintegration of cells. These specimens were not refused, however, and many are included in this series. Upper gastrointestinal tract barium studies frequently interfere, especially if the Roentgen examination was performed one or 2 days before the lavage or if retention is present.

In this series the lavage was not always performed by the same person; the preparation of the smear, however, was done in the same laboratory. The interpretation of the microscopic specimen was the responsibility of one physician.

It appears, therefore, that a routine mucolytic enzymatic gastric lavage with no special care taken to adhere strictly to optimal conditions, has definite value as a diagnostic procedure. The accuracy of this method can be increased by certain improvements in technique, as outlined above.

**Summary and Conclusions.** 1. The routine exfoliative cytologic laboratory procedure is again shown to be of definite value as an aid in establishing the diagnosis of gastric malignancies.

2. In a series of 70 patients with symptoms of upper gastrointestinal disease, 8 were proved histologically to have a malignancy of the stomach. By exfoliative cytology, 6 of these were detected. Four were diagnosed as "positive" for malignant cells, without equivocation.

3. Results from the use of this methodology can be improved by utilizing certain refinements in the technique which have been discussed.

4. Diagnoses rendered:

a. When an unequivocal cytologic diagnosis of malignancy was rendered, the accuracy in this study was 100%.

b. When cells were present which were felt to be diagnostically inconclusive, 25% of the patients proved to harbor a cancer.

c. When a negative report was rendered, 3% had carcinoma.

ACKNOWLEDGMENT: The authors wish to express their appreciation to T. L. Althausen, M.D., and to David A. Wood, M.D., for their cooperation and assistance in this program.

REFERENCES

1. **Bader, G. M.,** and **Papanicolaou, G. N.:** Cancer, **5,** 307, 1952.
2. **Farber, S. M., Benioff, M. A., Frost, J. K., Rosenthal, M.,** and **Tobias, G.:** Dis. Chest, **14,** 633, 1948.
3. **Graham, R. M.,** and **Meigs, J. V.:** Am. J. Obst. & Gynec., **58,** 843, 1949.
4. **Klayman, M. I.:** Personal communication.
5. **Lemon, H. M.:** New York State J. Med., **51,** 2155, 1951.
6. **Massey, B. W.,** and **Rubin, C. E.:** Am. J. M. Sci., **227,** 481, 1954.
7. **McDonald, J. R., Andujar, J., Clark, R. L., Collins, V. P., Guerriero, W. F.,** and **Hartman, A. W.:** Am. J. Clin. Path., **24,** 686, 1954.
8. **Papanicolaou, G. N.,** and **Traut, H. F.:** Am. J. Obst. & Gynec., **42,** 193, 1941.
9. **Rosenthal, M.,** and **Traut, H. F.:** Cancer, **4,** 1, 1951.
10. **Rubin, C. E.,** and **Benditt, E. P.:** To be published.
11. **Rubin, C. E., Massey, B. W., Kirsner, J. B., Palmer, W. L., and Stonecypher, D. D.:** Gastroenterology, **25,** 119, 1953.
12. **Rubin, C. E., Klayman, M. I.,** and **Kirsner, J. B.:** Med. Clin. N. America, **39,** 261, 1955.
13. **Traut, H. F., Rosenthal, M., Harrison, J. T., Farber, S. M.,** and **Grimes, O. F.:** Surg., Gynec., & Obst., **95,** 709, 1952.
14. **Ulfelder, G.:** New England J. Med., **241,** 236, 1949.
15. **Wisseman, C. L., Jr., Lemon, H. M.,** and **Lawrence, K. B.:** Surg., Gynec., & Obst., **89,** 24, 1949.

*(Interlingua on page 262)*

# EPIDEMIOLOGICAL ASPECTS OF CASES OF BLASTOMYCOSIS ADMITTED TO MEMPHIS, TENNESSEE, HOSPITALS DURING THE PERIOD 1922–1954: A REVIEW OF 86 CASES

By Ernest W. Chick, M.D.
SENIOR ASSISTANT SURGEON (R) KANSAS CITY FIELD STATION, CDC, USPHS, KANSAS CITY, KANSAS

Wheelan D. Sutliff, M.D.
CHIEF, INFECTIOUS DISEASE SECTION, VETERANS ADMINISTRATION TEACHING GROUP HOSPITAL (KENNEDY), MEMPHIS, TENNESSEE

Jennie H. Rakich, R.N.
NURSE OFFICER, KANSAS CITY FIELD STATION, CDC, USPHS, KANSAS CITY, KANSAS

AND

Michael L. Furcolow, M.D.
MEDICAL DIRECTOR, CHIEF, KANSAS CITY FIELD STATION, CDC, USPHS, KANSAS CITY, KANSAS

(From the Kansas City Field Station, Communicable Disease Center, U. S. Public Health Service, Kansas City, Kansas, and Veterans Administration Teaching Group Hospital [Kennedy], Memphis, Tennessee)

During December, 1954, the authors began the investigation of a small series of patients with blastomycosis, from the same geographical area, who were hospitalized in Memphis, Tennessee. A review of the hospital records of all hospitals in Memphis, going back as far as records were available, was considered desirable for three reasons: 1) to determine if there was any pattern of geographical location of the cases; 2) to determine if there were any recent cases, of which we were unaware, from the area of primary interest; 3) to determine the epidemiological aspects of the cases arising in this area which draws cases primarily from the southern states. These results could then be compared with previous reports.

The purpose of this paper is to present the epidemiological aspects of blastomycosis as determined in this series of patients. This is of general interest primarily because the source of infection by *Blastomyces dermatitidis* has never been demonstrated. To search intelligently for such a source, one must have information as to what type of individuals usually are infected, and what constitutional, environmental, geographical, and occupational differences there are in comparison to individuals who do not develop this disease. It is also hoped that this paper will serve to stimulate further interest in, and recognition of, blastomycosis, which, as seen by the large number of cases in Memphis, is not as uncommon as once believed.

**Materials and Methods.** Record librarians were contacted at 17 hospitals in Memphis*.

*John Gaston Hospital, Univ. of Tennessee, Methodist Hospital, Baptist Hospital, West Tennessee Tuberculosis Hospital, Oakville Sanatorium, Campbell Clinic, Collins Chapel Hospital, Terrell Memorial Hospital, St. Joseph Hospital, LeBonheur Childrens Hospital, Crippled Childrens Hospital, Crippled Adults Hospital, Memphis E.N.T. Hospital, Highland Hospital, McLemore Clinic, Public Health Service Marine Hospital, V. A. Med. Teaching Group Hospital, (Kennedy).

Psychiatric hospitals were not included. Each librarian was asked for information as to the number of cases of blastomycosis recorded in the files of their hospital. Ten hospitals reported no cases. Of the remaining 7, two had by far the highest number of cases (John Gaston Hospital and Kennedy Veterans Administration Hospital).

A total of 91 cases was found, the earliest recorded in 1922. Records of the individual cases were then reviewed with particular emphasis being placed on procedures for verification of the diagnosis, type of involvement, birthplace of the patient, place of residence at the time of admission to the hospital, age, sex, race, and occupation.

Three of the patients were outpatients who were not admitted to the hospital and therefore are not included in this series. For another 2 patients with vaguely described skin lesions but for whom microbiological studies were not done, the diagnosis of blastomycosis was made. These patients also are excluded from the series since recorded evidence was insufficient to warrant the diagnosis.

The series studied, therefore, is comprised of 86 patients in whom the diagnosis was made by means of smear, culture, biopsy, or a combination of these techniques.

TABLE 1.—DISTRIBUTION OF CLINICAL TYPES OF CASES OF BLASTOMYCOSIS ADMITTED TO MEMPHIS, TENNESSEE, HOSPITALS DURING THE PERIOD 1922 TO 1954.

| *Type of Involvement* | *Number of Cases* | *Per Cent of Cases* |
|---|---|---|
| Disseminating | 52 | 60.5 |
| Cutaneous | 23 | 26.7 |
| Pulmonary | 11 | 12.8 |
| Total | 86 | 100.0 |

**Results.** I. TYPE OF INVOLVEMENT. As shown by Table 1, in the present study the disseminated type* of blastomycosis was most commonly recorded with 60% of all cases falling in this group. The cutaneous form was next most common, accounting for 27% of all cases. Pulmonary involvement alone was found in 13%.

The literature presents somewhat variable values concerning the type of involvement in cases of blastomycosis. Fishman[9], in a review of 380 reported cases, found that only 19% were of the disseminated type. On the other hand, D'Aunoy and Bevan[4] found 40 to 50% of their cases to be of this type. They add that it is common for the systemic form of the disease to show cutaneous manifestations. In regard to symptoms apparent at onset, Martin and Smith[18] found that in 50% of their cases there was respiratory involvement, in 19% there were skin lesions, and in 23% subcutaneous nodules or abscesses had developed. A history of previous trauma was obtained in 4% of the cases they report. In the necropsied cases which they studied, 95% showed lesions in the lungs. This high incidence of pulmonary lesions gives added emphasis to Schwarz and Baum's postulation[22] that in blastomycosis, as in other fungous diseases such as histoplasmosis and coccidioidomycosis, the pulmonary involvement is primary and other manifestations are secondary to the lung lesion. Among dogs, studied in this connection by Menges[20] and other workers[10,27], all animals having blastomycosis showed pulmonary lesions.

A further breakdown regarding the organs involved in the disseminated form of the disease in this series of cases is given in Table 2. The lungs,

*Disseminated here is used to indicate the involvement of two or more organs or organ systems.

skin, and bone were most commonly involved, followed closely by the group of organs usually classified as the reticuloendothelial system: lymph nodes, liver, and spleen. Involvement of the genitourinary system was not uncommon. Three patients showed involvement of the central nervous system. Involvement of the larynx, the heart, and the gastrointestinal tract was noted in one case each. Evidence of involvement of an organ was based on the demonstration of the organism by smear or culture, or both, of exudate, sputum, gastric washing, biopsy, or necropsy material. An exception is the inclusion of bone involvement where the diagnosis was sometimes accepted on the basis of roentgenographic changes compatible with blastomycosis, and where the organism was demonstrated in another site.

TABLE 2.—DISTRIBUTION OF ORGAN OR ORGAN SYSTEM INVOLVEMENT IN CASES OF BLASTOMYCOSIS ADMITTED TO MEMPHIS, TENNESSEE, HOSPITALS DURING THE PERIOD 1922 TO 1954.

| *Organ or Organ System* | *Number of Cases* | *Per Cent of Cases* |
|---|---|---|
| Pulmonary | 49 | 57.0 |
| Cutaneous | 43 | 50.0 |
| Osseous | 20 | 23.2 |
| Reticuloendothelial | 15 | 17.4 |
| Genitourinary | 9 | 10.5 |
| Central nervous system | 3 | 3.5 |

TABLE 3.—LOCATION AT THE TIME OF ADMISSION OF CASES OF BLASTOMYCOSIS ADMITTED TO MEMPHIS, TENNESSEE, HOSPITALS, 1922 TO 1954.

| *State* | *Number of Cases* | *Per Cent of Cases* |
|---|---|---|
| Tennessee | 63 | 73.3 |
| Mississippi | 11 | 12.8 |
| Arkansas | 7 | 8.1 |
| Alabama | 2 | 2.3 |
| North Carolina | 2 | 2.3 |
| Illinois | 1 | 1.2 |
| Total | 86 | 100.0 |

II. GEOGRAPHICAL DISTRIBUTION. Table 3 depicts the geographical distribution of the cases at the time of admission to the hospital. As would be expected, the distance from the patient's home to the hospital is an important factor. Since Memphis is located in the southwest corner of Tennessee, it is in an advantageous position to draw from three neighboring states. When one considers the distribution of cases by county of residence (Fig. 1), the element of distance fom home to hospital becomes more apparent. It should be kept in mind also that large medical centers are located in all directions from Memphis (for example, St. Louis, Little Rock, New Orleans, Atlanta, and so forth) and that the farther from Memphis that a patient resided the closer he was to another center. Also a factor to be considered is that the Veterans Administration hospitalized 2 patients from North Carolina and the one from Illinois at its facility in Memphis rather than in their home areas.

Fifty-five of the 63 cases occurring in Tennessee listed Memphis as their

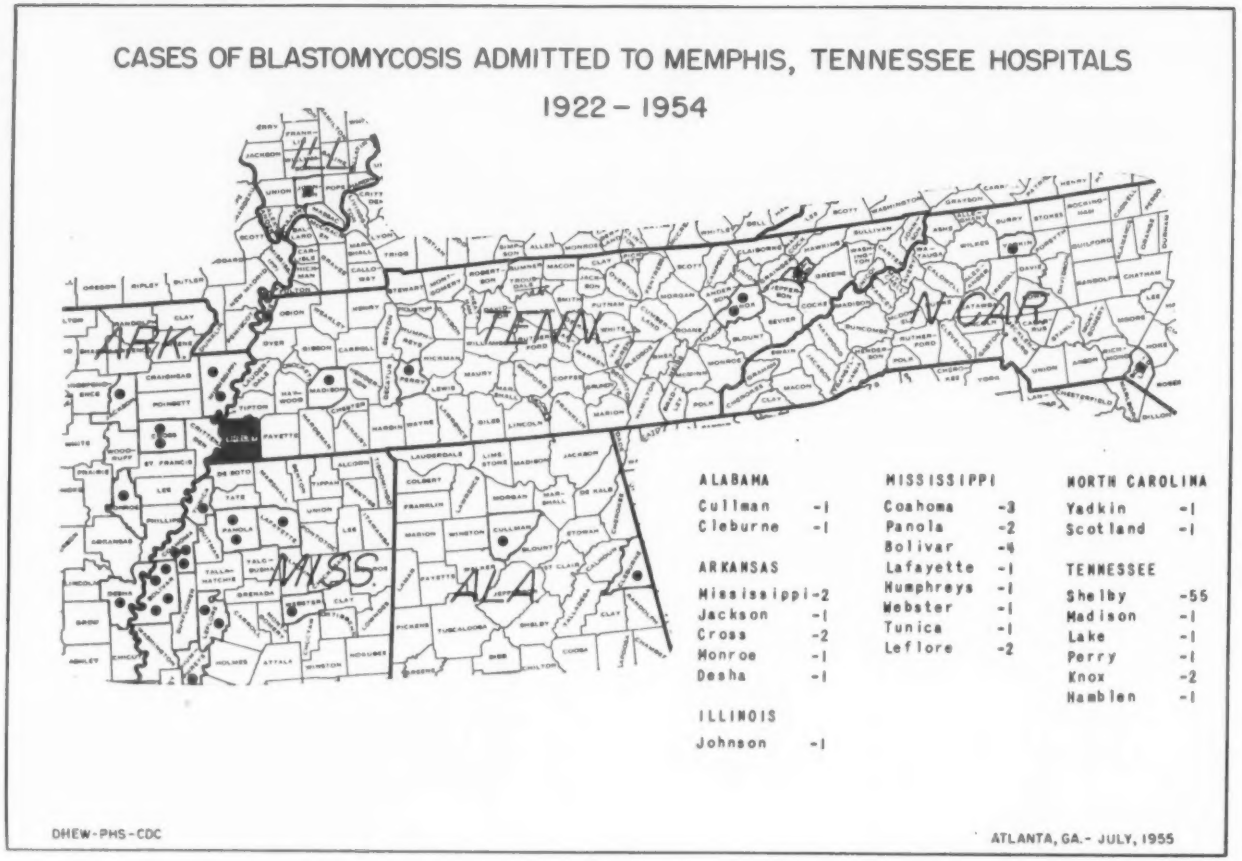
CASES OF BLASTOMYCOSIS ADMITTED TO MEMPHIS, TENNESSEE HOSPITALS
1922 – 1954
ILL.
ARK.
TENN.
N. CAR.
MISS.
ALA.
ALABAMA
Cullman -1
Cleburne -1
ARKANSAS
Mississippi -2
Jackson -1
Cross -2
Monroe -1
Desha -1
ILLINOIS
Johnson -1
MISSISSIPPI
Coahoma -3
Panola -2
Bolivar -4
Lafayette -1
Humphreys -1
Webster -1
Tunica -1
Leflore -2
NORTH CAROLINA
Yadkin -1
Scotland -1
TENNESSEE
Shelby -55
Madison -1
Lake -1
Perry -1
Knox -2
Hamblen -1
DHEW-PHS-CDC
ATLANTA, GA.- JULY, 1955

Fig. 1.

home. One wonders if this indicates a high incidence of infection within the boundaries of Memphis, or if listing a Memphis address facilitates hospital admission within the city. The listing of a Memphis address by a person from another area obviously would give a false impression of geographical distribution.

Table 4 gives the birthplaces of the cases by states. It is immediately apparent that the number of states listed as the place of birth is greater than the number listed as place of residence at the time of admission. Although the birthplace was unknown in 42% of the cases, of the data obtainable, one particular feature may be emphasized that although 73% of the cases listed Tennessee as their residence at the time of admission, only 10.5% of the cases are known to have been born in Tennessee. This would appear to lend weight to the previous question of the large number of cases listing Memphis as their residence. Unfortunately, this question remains unanswered at this time.

For the most part a comparison of the birthplace and the place of residence at the time of admission is invalid because of population movement during the past fifteen years. The length of time in each area of residence would provide more fruitful information. Unfortunately, this information is not available.

In the literature sporadic cases have been reported throughout the North American continent[18,24,25,26,34]. Most of the cases, however, have been reported from the Midwest, the Ohio River Valley, and the Southeast[22].

III. AGE DISTRIBUTION. The age distribution of our cases is shown in Table 5. In 23% of the cases, the infection occurred before the age of 30 years; in 43%, between the ages of 31 and 50 years; and in 34% after the age of 50 years. The largest group of cases (30.2%) were between the ages of 26 and 35 years.

In the series of cases reported by Martin and Smith[18] the age of individuals at the time of diagnosis was from 6 months to 70 years or older. They found that 50% of their cases with systemic infection were between the ages of 20 and 40 years while the age distribution for the cases of cutaneous infection was somewhat greater. In Schwarz and Goldman's recent series

TABLE 4.—BIRTHPLACE, ACCORDING TO STATE, OF CASES OF BLASTOMYCOSIS ADMITTED TO MEMPHIS, TENNESSEE, HOSPITALS DURING THE PERIOD 1922 TO 1954.

| *State* | *Number of Cases* | *Per Cent of Cases* |
|---|---|---|
| Mississippi | 21 | 24.4 |
| Tennessee | 9 | 10.5 |
| Arkansas | 6 | 7.0 |
| Louisiana | 3 | 3.5 |
| Ohio | 1 | 1.2 |
| Texas | 1 | 1.2 |
| North Carolina | 2 | 2.3 |
| Illinois | 1 | 1.2 |
| Missouri | 2 | 2.3 |
| Oklahoma | 2 | 2.3 |
| Georgia | 2 | 2.3 |
| Unknown | 36 | 41.8 |
| Total | 86 | 100.0 |

Fig. 1.

of 101 patients[25], 40% were between the ages of 30 and 49 years, and 49% were over 50 years of age.

IV. SEX DISTRIBUTION. Of the 86 cases in our series 87% occurred in males and 13% in females. Martin and Smith[18] found an over-all ratio of 9 males to 1 female. In their systemic cases, 92% were males, and in patients with only skin or local lesions 80% were males. Schwarz and Goldman[25] found 88% of their series were males.

V. RACIAL DISTRIBUTION. There was a predominance of Negro patients in this series, with 69% being colored and 31% being white. This proportion of colored cases is greater than would be expected when compared to the ratio of white to colored in the total population of this area (Table 6).

Martin and Smith's series[18] showed a distribution of 28% colored patients and 72% white. Of their white cases, 54% were of foreign extraction. In the present series of 86 patients, 58.2% were born in the United States. The birthplace is unknown in the remainder. In Schwarz and Goldman's series[25] only 15% of the patients were colored.

TABLE 5.—AGE DISTRIBUTION OF CASES OF BLASTOMYCOSIS ADMITTED TO MEMPHIS, TENNESSEE, HOSPITALS DURING THE PERIOD 1922 TO 1954.

| *Age* | *Number of Cases* | *Per Cent of Cases* |
|---|---|---|
| 0–5 | 1 | 1.2 |
| 6–10 | 2 | 2.3 |
| 11–15 | 0 | 0 |
| 16–20 | 3 | 3.5 |
| 21–25 | 3 | 3.5 |
| 26–30 | 11 | 12.8 |
| 31–35 | 15 | 17.4 |
| 36–40 | 7 | 8.1 |
| 41–45 | 9 | 11.5 |
| 46–50 | 6 | 7.0 |
| 51–55 | 9 | 10.5 |
| 56–60 | 5 | 5.8 |
| 61–65 | 8 | 9.3 |
| 66–70 | 4 | 4.6 |
| 71– | 3 | 3.5 |
| Total | 86 | 100.9 |

TABLE 6.—POPULATION* OF STATES BY RACE AND SEX WITH THE MAJORITY OF CASES OF BLASTOMYCOSIS ADMITTED TO MEMPHIS, TENNESSEE, HOSPITALS DURING THE PERIOD 1922 TO 1954.

| | | *All Classes by Per Cent* | | | *White by Per Cent* | | | *Nonwhite by Per Cent* | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *State* | *Population* | *Total* | *Male* | *Female* | *Total* | *Male* | *Female* | *Total* | *Male* | *Female* |
| Tennessee | 3,291,718 | 100.0 | 49.3 | 50.7 | 83.9 | 49.5 | 50.5 | 16.1 | 48.2 | 51.8 |
| Alabama | 3,061,743 | 100.0 | 49.1 | 50.9 | 67.9 | 49.7 | 50.3 | 32.1 | 47.8 | 52.2 |
| Mississippi | 2,178,914 | 100.0 | 49.4 | 50.6 | 54.6 | 50.1 | 49.9 | 45.4 | 48.6 | 51.4 |
| Arkansas | 1,909,511 | 100.0 | 49.8 | 50.2 | 77.6 | 50.2 | 49.8 | 22.4 | 48.6 | 51.4 |

*Census 1950.

VI. OCCUPATION. The occupations of the cases are shown in Table 7. Thirty-three per cent were classified as laborers, 17% as agricultural workers, and 13% as white collar workers (clerks, waiters, barbers, salesmen, and lawyers), while for 37% the occupation was unknown. As has been noted frequently[11,15,18,36], the majority of cases of blastomycosis occur in persons

whose work puts them outdoors or in cantact with products of the outdoors. Starrs and Klotz[34] state, "it most commonly infects agricultural workers, common laborers, and persons who work or live in damp, dirty, or wooded places."

VII. MORTALITY. Unfortunately, many of the records reviewed in this series of cases did not include a complete follow-up history. Some of the patients were seen only once and did not return as scheduled, or left the hospital against advice during the course of treatment. Others apparently had a remission, were discharged and for varying reasons were not seen again in the clinic. Twenty-six and seven-tenths per cent of the patients are known to have expired while under treatment for blastomycosis, but for the reasons given above this is believed to be less than the deaths which probably occurred as a result of this disease.

In Schwarz and Goldman's series[25] of 101 patients only 3% died during the period of observation, although 51% were classified as having generalized disease. Martin and Smith[18] estimated the mortality from this disease to be 78 to 92%, and Fishman[9] 83%.

VIII. EPIDEMICS. The first culturally proven epidemic of blastomycosis has recently been reported by Smith *et al.*[32]. Ten persons from a small town in North Carolina developed systemic blastomycosis during a 6-month period. The ages of the cases were of especial note in that 7 were under 16 years of age. In spite of exhaustive attempts to isolate the organism from the environment, the source of this epidemic remains unknown. The authors concluded that "exposure to a common respiratory mode of transmission seemed more likely than infection through cutaneous contact or from person to person."

Four cases of blastomycosis with onsets over a somewhat greater time span have occurred in Bolivar County, Mississippi, and are being studied by us at present. No common source of infection has been determined. At present, soil samples are being cultured in an attempt to isolate the organism.

TABLE 7.—OCCUPATION DISTRIBUTION OF CASES OF BLASTOMYCOSIS ADMITTED TO MEMPHIS, TENNESSEE, HOSPITALS DURING THE PERIOD 1922 TO 1954.

| *Occupation* | *Number of Cases* | *Per Cent of Cases* |
|---|---|---|
| Laborer | 29 | 33 |
| Agricultural | 15 | 17 |
| White collar | 11 | 13 |
| Unknown | 31 | 37 |

**Discussion.** From the data obtained in the review of this series of 86 cases, it is possible to propose a composite typical patient with blastomycosis who might be seen in a Memphis hospital. The patient would be a colored male early in his fifth decade of life. His occupation would be that of a laborer. His home would be listed as Tennessee, very likely Memphis, although his birthplace probably would be in Mississippi. He would have the disseminated form of blastomycosis with pulmonary and cutaneous lesions and, quite likely, bone lesions as well.

Obviously the above composite picture is subject to many erroneous interpretations. For example, the listing of a Memphis address has already been discussed. However, such a composite picture lends itself to some interesting

speculations regarding the epidemiology of blastomycosis.

The patient would be a male, therefore the route of infection would necessarily be one to which this sex is more easily accessible. The race would be colored (although as has been shown, this varies with geographic locale). His occupation would be a laborer. (In the Memphis area a large proportion of common laborers, percentage wise, would be colored males.) Therefore, the route of infection appears to be one that would be common to laborers or to persons engaged in related occupations.

This is given further emphasis by the following observations. Cases of blastomycosis occur sporadically most commonly. On this basis, one must assume that either *B. dermatitidis* is not transmitted by vehicles such as food, water, sewage, and so forth, that tend to infect large numbers of persons, and more particularly infect a wider range of persons as regards age and sex, or that if *B. dermatitidis* can be transmitted by these means, it has a low and a rather selective rate of infectivity. Person-to-person transmission has not been reported. Schwarz and Baum[23] studied contacts of patients with blastomycosis (58 hospital workers and 48 home contacts) by means of skin tests. All had negative reactions, giving further evidence against person-to-person spread.

The common denominator for the various occupations grouped under the classification of common laborer is an intimate, physical contact with products of nature, soil (ditch-diggers, road repair and construction workers, and others), wood (carpenters, loggers, and others), and agricultural products (tobacco and cotton factory workers, and the like). Therefore, it would appear that the mode of infection of *B. dermatitidis* is related to work with some form or forms of natural products. This is given further emphasis by the fact that the next highest percentage of cases according to occupation in this series was agricultural.

If one analyzes the concept of a natural product further to find a common basic factor, that factor proves to be soil. Emmons[8] has described soil as a "broad mixture of organic debris decaying plant material, humus, excreta, and keratinaceous and proteinaceous remains of insects, birds and animals, and the vast and varied microflora and microfauna of soil." That *Histoplasma capsulatum*[1,6,12,17] and *Coccidioides immitis*[5,29] occur in soil and cause infection therefrom is now an accepted fact. Soil is thought to be of primary importance in the pathogenesis of infection by various other fungi including *Allescheria boydii*[1], *Microsporum gypseum*[1], and *Cryptococcus neoformans*[7]. *B. dermatitidis* has been held suspect as occurring in soil or soil products since the report of Stober[36] but as yet has not been isolated from this medium. On several occasions Stober isolated an organism resembling *B. dermatitidis* from decaying wooden walls in the living quarters of patients with blastomycosis, but satisfactory proof by cultural methods was not obtained. Emmons[8] and this laboratory[21], however, have demonstrated that *B. dermatitidis* will grow in the laboratory in soil or bark which has been previously autoclaved and then inoculated with this organism.

The primary pulmonary involvement in histoplasmosis[12,14,16,17,26] and coccidioidomycosis[26,28,29,30] from soil infection is well known. It has been postulated that pulmonary involvement may be primary in blastomycosis also[3,20,22,24]. If the cutaneous form is accepted as occurring without other visceral involvement, the usual history is one of injury to the skin, with the injured

area becoming contaminated by soil or soil products, and with the subsequent development of a blastomycotic lesion at the site of trauma. This, with the epidemiological factors above, strongly incriminates soil or soil products as the mode of transmission of *B. dermatitidis*. The fact that *B. dermatitidis* has not been isolated from soil, despite numerous attempts, weakens this postulation, if one assumes that the techniques used are adequate. On the basis of the available knowledge, it seems that soil or soil products are to be the most strongly incriminated as the source of infection with blastomycosis, and that our inability to isolate *B. dermatitidis* from soil indicates the inadquacy of present techniques.

**Summary.** A series of 86 cases of blastomycosis admitted to Memphis, Tennessee, hospitals during the period 1922 to 1954 is presented.

Epidemiological aspects of these cases including geographical distribution, age, sex, race, and occupation are illustrated, and comparisons are made with cases recorded in the literature.

A discussion is given concerning the logic of interpreting these data to incriminate soil or soil products as the primary source of *Blastomyces dermatitidis* and direct contact as the usual mode of transmission.

ACKNOWLEDGMENT. The authors would like to acknowledge the assistance of Dr. L. M. Graves, Director of the Memphis-Shelby County Health Office, who greatly facilitated the procurement of this material.

## REFERENCES

1. **Ajello, L.:** Am. J. Trop. Med. & Hyg., **3**, 897, 1954.
2. **Benham, R. W.:** Ann. New York Acad. Sci., **50**, 1299, 1950.
3. **Carter, R. A.:** Radiology, **26**, 551, 1936.
4. **D'Aunoy, R., and Bevan, J. L.:** J. Lab. & Clin. Med., **16**, 124, 1930.
5. **Emmons, C. W.:** Pub. Health Rep., **57**, 109, 1942.
6. Idem: Ibid., **64**, 892, 1949.
7. Idem: J. Bacteriol., **62**, 685, 1951.
8. Idem: New York Acad. Sci., **14**, 51, 1951.
9. **Fishman, J.:** U. S. Naval Med. Bull., **43**, 758, 1944.
10. **Foshay, L., and Madden, A. G.:** Am. J. Trop. Med., **22**, 565, 1942.
11. **Friedman, L. L., and Signorelli, J. J.:** Ann. Int. Med., **24**, 385, 1946.
12. **Furcolow, M. L., and Larsh, H. W.:** Proc. Soc. Exper. Biol. & Med., **80**, 246, 1952.
13. **Goldman, L., and O'Hara, H.:** Rev. argent. dermatosif., **34**, 131, 1950.
14. **Grayston, J. T., and Furcolow, M. L.:** Am. J. Pub. Health, **43**, 665, 1953.
15. **Greiner, D. J.:** J. Tennessee State Med. Assn., **43**, 156, 1950.
16. **Ibach, M. J., Larsh, H. W., and Furcolow, M. L.:** Proc. Soc. Exper. Biol. & Med., **85**, 72, 1954.
17. **Kier, J. H., Campbell, C. C., Ajello, L., and Sutliff, W. D.:** J. Am. Med. Assn., **155**, 1230, 1954.
18. **Martin, D. S., and Smith, D. T.:** Am. Rev. Tuberc., **39**, 275, 1939.
19. **McVay, L. V., and Carroll, D. S.:** Am. J. Med., **12**, 289, 1952.
20. **Menges, R. W., McClellan, J. T., and Ausherman, R. J.:** J. Am. Vet. Med. Assn., **124**, 202, 1954.
21. **Menges, R. W., Furcolow, M. L., Larsh, H. W., and Hinton, A.:** J. Infect. Dis., **90**, 67, 1952.
22. **Schwarz, J., and Baum, G. L.:** Am. J. Clin. Path., **21**, 999, 1951.
23. Idem: J. Invest. Dermat., **18**, 3, 1952.
24. Idem: Docum. med. geog. et trop., **5**, 29, 1953.
25. **Schwarz, J., and Goldman, L.:** A.M.A. Arch. Dermat., **71**, 84, 1955.
26. **Schwarz, J., and Furcolow, M. L.:** Am. J. Clin. Path., **25**, 261, 1955.
27. **Seibold, H. R.:** North Am. Veterinarian, **27**, 162, 1946.
28. **Smith, C. E.:** Am. J. Pub. Health, **30**, 600, 1940.

29. Idem: Med. Clin. N. America, **27**, 790, 1943.
30. **Smith, C. E., Beard, R. R., Rosenberger, H. G.,** and **Whiting, E. G.:** J. Am. Med. Assn., **132**, 833, 1946.
31. **Smith, D. T.:** Ann. Int. Med., **31**, 463, 1949.
32. **Smith, J. G., Harris, J. S., Conant, N. F.,** and **Smith, D. T.:** J. Am. Med. Assn., **158**, 641, 1955.
33. **Snapper, I.,** and **McVay, L. V.:** Am. J. Med., **15**, 603, 1953.
34. **Starrs, R. A.,** and **Klotz, M. O.:** A.M.A. Arch. Int. Med., **82**, 1, 1948.
35. Iidem: Ibid., **82**, 29, 1948.
36. **Stober, A. M.:** Ibid., **13**, 509, 1914.
37. World Almanac and Book of Facts for 1955, H. Hansen, editor, New York: New York World-Telegram, 1955.

## SUMMARIO IN INTERLINGUA

### Aspectos Epidemiologic de Casos de Blastomycosis Admittite Durante le Periodo 1922–1954 al Hospitales del Citate de Memphis, Tennessee

Es presentate un serie de 86 casos de blastomycosis admittite inter 1922 e 1954 a hospitales de Memphis in Tennessee.

Es illustrate aspectos epidemiologic de iste casos, includente distribution geographic, etate, sexo, racia, e occupation. Le datos es comparate con casos reportate in le litteratura.

Es discutite le bases logic de interpretar tal datos de maniera a incriminar le solo e productos del solo como fonte primari de *Blastomyces dermatitidis* e contacto directe como le forma normal del transmission.

## SUMMARIO IN INTERLINGUA

*(See page 249 for original article)*

### Exfoliative Cytologia Gastric

1. Es monstrate de novo que le routine laboratorial de exfoliative cytologia gastric es de valor definite como adjuta in establir le diagnose de malignitates gastric.

2. In un serie de 70 patientes con symptomas de morbo gastrointestinal superior, il esseva demonstrate per medios histologic que 8 habeva un malignitate gastric. In quatro casos le diagnose de cellulas maligne esseva inequivocamente positive.

3. Es discutite certe raffinamentos technic que resulta in meliorate constatationes obtenite per iste methodologia.

4. Tabulation diagnostic:

a. Quando un inequivoc diagnose cytologic de malignitate esseva obtenite, le exactitude diagnostic (in le presente studio) esseva 100 pro cento.

b. Quando cellulas esseva presente que impressionava nos como diagnosticamente indecise, 25 pro cento del patientes permitteva le demonstration de cancere.

c. Quando le reporto diagnostic esseva negative, 3 pro cento del patientes habeva carcinoma.

# JOINT AND BONE DISEASE DUE TO MYCOTIC INFECTION*

By Elam C. Toone, Jr., M.D.
ASSOCIATE PROFESSOR OF MEDICINE

AND

John Kelly, M.D.

(From the Department of Medicine, Medical College of Virginia, and the Medical Service, McGuire Veterans Hospital, Richmond, Virginia)

The importance of pathogenic fungi as a cause of bone and joint disease has taken on added significance as the result of several developments. First, the control of pathogenic bacteria with chemotherapeutic and antibiotic agents has increased the relative frequency. Second, increased travel incident to military service and other factors has resulted in a dissemination of fungus infections. Third, therapeutic agents of a more effective nature for several of the mycotic organisms have become available recently.

Twenty-five cases of fungus disease observed at the McGuire Veterans Hospital and the Hospital Division of the Medical College of Virginia in a 5-year period from 1949 through 1954 have been reviewed. These included 11 cases of blastomycosis, 4 of coccidioidomycosis, 4 of cryptococcosis, 3 of actinomycosis, 2 of histoplasmosis and 1 of nocardiosis. In 8 cases there was involvement of bone or joint (Table 1).

The incidence of mycotic infection is much larger than is generally appreciated[3,13]. The types of infection encountered here are about as anticipated for this area, with the possible exception of the 4 cases of coccidioidomycosis. Each of these, however, gave a history of having traveled or maintained a residence in one of the endemic areas of California. The age range varied between 18 and 59 years, and was not felt to be unusual. There was only one female patient in the group of 25 cases. This correlates with the general predominance of systemic fungus infections in males, but the series could not be considered representative, since 18 of the 25 cases were observed at the McGuire Veterans Hospital which had an almost negligible number of female patients. Fourteen patients were white and 11 Negro, and there was no evidence of racial susceptibility except in the 4 cases due to coccidioidomycosis infection. Three of these 4 cases were among Negroes, and in 2 of these the disease was disseminated and progressive. The deeply pigmented races have been found to be more susceptible to this infection, and the disease is usually more serious[1,3]. There has been a pop-

TABLE 1.

| *Fungus Disease* | *Total No. of Cases* | *No. of Cases with Bone Involvement* |
|---|---|---|
| Actinomycosis | 3 | 0 |
| Blastomycosis | 11 | 5 |
| Coccidioidomycosis | 4 | 1 |
| Cryptococcosis | 4 | 2 |
| Histoplasmosis | 2 | 0 |
| Nocardiosis | 1 | 0 |
| Total | 25 | 8 |

*Presented at the American Clinical and Climatological Association, November 1, 1955, Hot Springs, Virginia.

ular, although probably incorrect, conception that systemic fungus disease is restricted to rural areas, and to individuals in the lower income groups. In this series, 14 patients were from rural areas: 8 farmers, 5 laborers, and one Pullman porter. Eleven patients were from urban centers: 3 laborers, 2 executives, one teacher, one policeman, one clerk, one student, one textile worker, and one who at the moment was unemployed but who had been discharged recently from the United States Marine Corps (Table 2).

TABLE 2.

| *Patient* | *Age* | *Sex* | *Race* | *Occupation* | *Residence* | *Diagnosis* | *Bone Involvement* | *Involvement Other Than Bones* |
|---|---|---|---|---|---|---|---|---|
| S.E. | 30 | M | W | Farmer | Rural | Actinomycosis | 0 | Cervical nodes |
| M.R. | 41 | M | W | Farmer | Rural | Actinomycosis | 0 | Cervical nodes |
| J.R. | 23 | M | W | Lumber mill worker | City | Actinomycosis | 0 | Cervical nodes |
| W.D. | 29 | M | W | Laborer | Rural | Blastomycosis | 0 | Lungs and skin |
| M.G. | 47 | M | W | Executive | City | Blastomycosis | 0 | Lung |
| K.U. | 40 | M | C | Laborer | Rural | Blastomycosis | + | Lungs |
| J.D. | 57 | M | C | Laborer | Rural | Blastomycosis | + | Disseminated |
| C.T. | 59 | M | W | Farmer | Rural | Blastomycosis | + | Disseminated |
| A.H. | 59 | M | C | Farmer | Rural | Blastomycosis | 0 | Disseminated |
| R.M. | 59 | M | W | Lumberman | Rural | Blastomycosis | 0 | Skin |
| E.T. | 32 | M | C | Farmer | Rural | Blastomycosis | 0 | Disseminated |
| I.B. | 43 | M | W | Policeman | City | Blastomycosis | + | Disseminated |
| E.T. | 32 | M | C | Farmer | Rural | Blastomycosis | 0 | Disseminated |
| J.T. | 23 | M | W | Textile worker | City | Blastomycosis | + | Lungs |
| U.H. | 37 | M | C | Pullman porter | Rural | Coccidioidomycosis | 0 | Disseminated |
| M.D. | 43 | M | C | Farmer | Rural | Coccidioidomycosis | + | Lungs |
| W.J. | 37 | M | C | Carpenter | Rural | Coccidioidomycosis | 0 | Lung |
| J.W. | 24 | M | W | Store clerk | City | Coccidioidomycosis | 0 | Lung |
| J.H. | 35 | M | W | Executive | City | Cryptococcosis | 0 | Lung |
| R.J. | 18 | F | C | Student | City | Cryptococcosis | + | Disseminated |
| A.P. | 44 | M | C | Laborer | City | Cryptococcosis | 0 | Meninges |
| B.G. | 27 | M | C | Farmer | Rural | Cryptococcosis | + | Disseminated |
| H.S. | 31 | M | W | Laborer | City | Histoplasmosis | 0 | Lung |
| A.C. | 46 | M | W | Teacher | City | Histoplasmosis | 0 | Lungs and skin |
| J.B. | 24 | M | W | None | City | Nocardiosis | 0 | Disseminated |

Of the total number of 25 cases reviewed, three types of mycotic organisms produced joint and bone lesions. These were *Blastomyces dermatitidis, Cryptococcus neoformans,* and *Coccidioides immitis.* A brief review of the disease pattern produced by these organisms will be made and representative case histories presented (Table 3).

BLASTOMYCOSIS[1,3,6,13]. North American blastomycosis is probably limited to the United States and Canada. The causative organism is the *Blastomyces dermatitidis* which is a single budding, yeast-like cell with a thick refractile wall. The source of this organism and its mode of invasion are unknown. The infection may take either of two clinical forms: cutaneous or systemic. In the systemic form, the skin, lungs and bones are chiefly involved, with the latter occurring probably in over half of the cases. Any of the bones of the body may be affected, but the cancellous more often than the tubular. The process is usually an osteolytic one with little or no surrounding bone reaction or production. Recent reports have

shown that stilbamidine and 2-hydroxystilbamidine have been effective therapeutic agents.

**Case Reports.** CASE 1. J. D., a 50-year-old Negro male was admitted to St. Philip Hospital, of the Medical College of Virginia, on September 14, 1954. The general health had been good until 6 weeks prior to admission at which time multiple furuncles in the region of the right wrist, right great toe, and the dorsum of the left foot developed. One week prior to admission pain, swelling and redness developed in the right knee, both ankles and the right wrist. For 2 weeks there had been slight anorexia, malaise and a low grade fever. *Physical examination* revealed that draining sinuses of the right wrist, right great toe and dorsum of the left foot were present. There was painful swelling and redness of both ankles, the right knee and right wrist. Both the liver and spleen were barely felt on deep inspiration. Inspiratory and expiratory crepitant rales were heard in both lung bases. *Laboratory data:* A direct smear from the sinus of the right wrist area was positive for *Blastomyces dermatitidis*. The hemoglobin was 7.8 gm.; erythrocytes, 2,620,000; leukocytes, 17,400; polymorphoneutrophils, 97%. A urinalysis showed an albumin of 1 plus, and many white cells in the sediment. Six blood cultures were negative, and three sputum specimens showed no tubercle bacilli. *Roentgenographic examinations:* There was extensive bone destruction of the distal third of the right ulna with a pathologic fracture present, moderate destruction of the proximal phalanx of the right great toe, a few punched out areas in the region of the right sacroiliac joint, a mottled "moth-eaten" appearance of the bodies of L–3 and L–4 vertebrae with necrosis and fracture of the transverse process of L–4 and moderate destruction of the right patella. A chest film showed mottled infiltration throughout the right lung field and the mid zone of the left. There was a small amount of fluid in the right costophrenic angle. *Course in hospital:* The patient was considered acutely ill at the time of admission, and died 4 days after entering the hospital. A single, 100-mg. dose of 2-hydroxystilbamidine was given intravenously on the day prior to death without any noticeable clinical effect (Figs. 1 and 2).

TABLE 3.

| *Patient* | *Diagnosis* | *Extent of Bone Involvement* |
|---|---|---|
| K.U. | Blastomycosis | Right patella and tibia |
| J.D. | Blastomycosis | Right ulna, proximal phalanx of right great toe, right sacro-iliac joint and 3rd and 4th lumbar vertebræ |
| C.T. | Blastomycosis | Cuneiforms, scaphoid, cuboid and the 1st, 2nd, and 3rd metatarsals of the left foot |
| I.B. | Blastomycosis | Sacrum |
| J.T. | Blastomycosis | Talus, calcaneous, tarsals and the 2nd and 3rd cuneiforms of right foot |
| M.D. | Coccidioidomycosis | Cervical and dorsal vertebræ |
| R.J. | Cryptococcosis | Ribs, sternum and pelvis |
| B.G. | Cryptococcosis | Skull, pelvis, right acromial process, right humerus, right tibia and the right 1st metacarpal |

CRYPTOCOCCOSIS[2,7,15]. Cryptococcosis is world-wide in distribution. The infection is caused by the *Cryptococcus neoformans*, a single budding yeast-like cell, with a thick capsule which can be clearly demonstrated by an India ink preparation. The organism has a known saprophytic existence in nature, but the mode of invasion in man is not understood. The disease has a marked predilection for the central nervous system, but the skin, lungs and other organs may also be affected. Joint and bone involvement is said to be rare, but does occur. The process is almost purely an osteolytic one with little or no reaction occurring in the surrounding bone or periosteum, and no tendency to bone production. There seems to be an affinity for various bony prominences; otherwise, almost any bone in the body may be affected. Encouraging results in treatment with stilbamidine and 2-hydroxystilbamidine have been reported recently, although the organism does not appear to be influenced as strongly by these drugs as does the *Blastomyces dermatitidis*.

**The central nervous system involvement is particularly resistant to treatment.**

CASE 2. B. G., a 27-year-old Negro male was admitted to St. Philip Hospital, of the Medical College of Virginia, on January 20, 1953. There had been a cough productive of clear sputum for 5 months, and pain, swelling and limitation of motion of the right shoulder for 2. There was an additional history of weight loss, malaise, and temperature elevation. At the age of 5 years, osteomyelitis of the right leg had developed following trauma, and the use of a leg brace since that time had been necessary. *Physical examination:* The temperature was 103.2° F., the skin was hot and dry, and the patient was described as being lethargic. A tender, fluctuant, 8- by 3-cm. mass was present over the right acromial process. There was a moderate generalized discrete lymphadenopathy, and the spleen was barely palpable. *Laboratory data:* The *Cryptococcus neoformans* was found on smear and culture in material aspirated from a mass over the acromium and on culture of the urine. The urine otherwise was negative except for a slight amount of

Fig. 1.—Table 3, Case 2. Osteolytic changes, distal one-third of right radius and ulna with pathologic fracture of right ulna. Blastomycosis. Died. (Case Report 1.)

albumin. There was a persistent eosinophilia of 10%, but the hemogram otherwise was not remarkable. Spinal fluid examination was entirely normal. *Roentgenographic examinations:* Sharply defined punched out areas were present in the skull, proximal end of the first left metacarpal, the right acromial process, the shaft of the right humerus, and in several ribs. There was also extensive widening and thickening of the right tibia indicative of marked bone productive changes, and probably resulting from the old osteomyelitis, presumably bacterial. Chest roentgenogram showed a moderate hilar adenopathy, and a moderate degree of diffuse fibrosis. *Hospital course:* Initial treatment consisted of the use of symptomatic and supportive measures with no appreciable change in the clinical status, and the patient left the hospital against medical advice after one week. He returned 6 weeks later after having developed fluctuant masses over the forearm and sternum. *Cryptococcus neoformans* was cultured from these areas as well as from the sputa, and the urine continued positive. Treatment with 2-hydroxystilbamidine intravenously was then instituted for 20 days in a daily dose of 225 mg. Following a rest period of 10 days, this same course of treatment was repeated. Clinical improvement was prompt and quite marked with a return of temperature to normal, weight gain, disappearance of malaise, and the disappearance of the fluctuant masses in the various areas mentioned. A 2-months' follow-up roent-

Fig. 2.—Table 3, Case 5. Osteolytic changes with extensive destruction of the right foot. Treatment: iodides and Roentgen-ray. Recovery. Blastomycosis.

genographic study of the bones, however, showed no change. This is a characteristic experience. The patient was last seen 6 months following therapy, and appeared to be doing well clinically; but efforts to have him return to the hospital for more detailed studies have not been successful. His present status is not known although casual information obtained from friends and members of the family indicates that his condition is quite satisfactory (Figs. 3 and 4).

Fig. 3.—Table 3, Case 8. Osteolytic changes in the skull. Treatment: 2-hydroxystilbamidine. Recovery. Cryptococcosis. (Case Report 2.)

COCCIDIOIDOMYCOSIS[1,4,8,12]. Coccidioidomycosis is endemic in the southwestern part of the United States, and is particularly prevalent in the San Joaquin Valley region of California. The causative agent is the *Coccidioides immitis* which is a round, thick-walled organism containing numerous endospores. It is found in the soil, and it is believed that invasion occurs by inhalation. The disease takes one of two forms: the benign pulmonary infection or the chronic, progressive, and often fatal, systemic. In the latter, the skin, bones, and other organs may be involved by spread from the original pulmonary infection which usually is progressive. Bone lesions are quite common, and usually appear as cyst-like areas of osteolysis. Proliferative periostitis may be present, although frequently there is no surrounding bone reaction. To date no effective therapy has been reported for the progressive systemic type of coccidioidomycosis.

CASE 3. M. D., a 42-year-old Negro male farmer, while serving with the Army at Mather Field, California, in 1946, had been found to have an infiltration of the left lung

field which was presumed to be tuberculosis, although no organism was identified. For the next year symptomatic treatment was instituted with improvement of the pulmonary infiltration, but with the appearance of a destructive process involving several of the dorsal vertebrae. Shortly after discharge from the Army in 1947, he entered a Veterans Administration hospital. No definite diagnosis was established, but a year's therapy with streptomycin and para-aminosalicylic acid was given. Nine months following this course of treatment a fluctuant mass in the upper dorsal region became evident. In 1950, he was admitted to McGuire Veterans Hospital, in Richmond, Virginia, because of this, and the mass was incised and drained. Smear and culture of the purulent material obtained were positive for *Coccidioides immitis*. Symptomatic and supportive treatment was continued, principally at home, and the process apparently became stable. In 1951, he was recalled to McGuire Veterans Hospital for further evaluation. There were two small draining sinuses

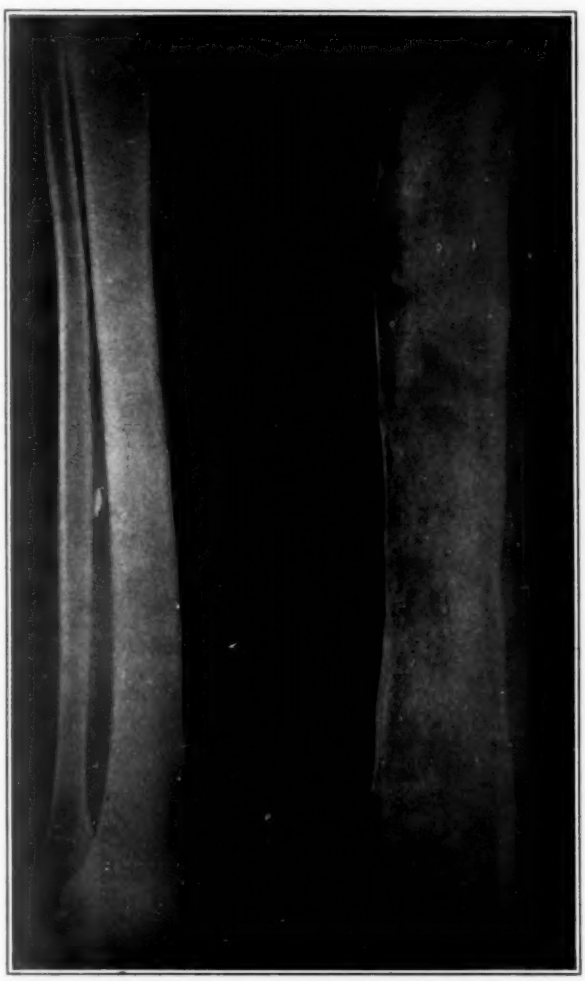

Fig. 4.—Table 3, Case 8. Extensive bone productive changes of right tibia following bacterial osteomyelitis in childhood. Illustrates, in the same patient, osteolytic changes due to mycotic infection and bone productive changes due to bacterial infection. (Case Report 2.)

present in the upper right dorsal region of the back, and complete fixation of the cervical spine. *Laboratory studies*: Smear and culture made from material removed from the draining sinuses were positive for *Coccidioides immitis*. The hemoglobin was 8.9 gm.; erythrocytes, 3,090,000; leukocytes, 15,000 with a normal differential count. The urine showed a 3 plus albuminuria and was otherwise negative. *Roentgenographic examinations:* The chest roentgenogram was reported as being negative, and showed no evidence of any residual infiltration. The cervical and dorsal spine showed productive bone changes with bridging between the last four cervical vertebrae. There was evidence of bone destructive and productive changes in the seventh, eighth and ninth dorsal vertebrae. Shortly thereafter the patient left the hospital against medical advice. In November, 1953, the patient was admitted to another Veterans Administration hospital, and expired the following day. Postmortem examination showed a large paravertebral abscess in the right upper dorsal area with bone destructive and productive changes in the lower cervical and upper dorsal vertebrae. *Coccidioides immitis* was identified in the material obtained (Figs. 5 and 6).

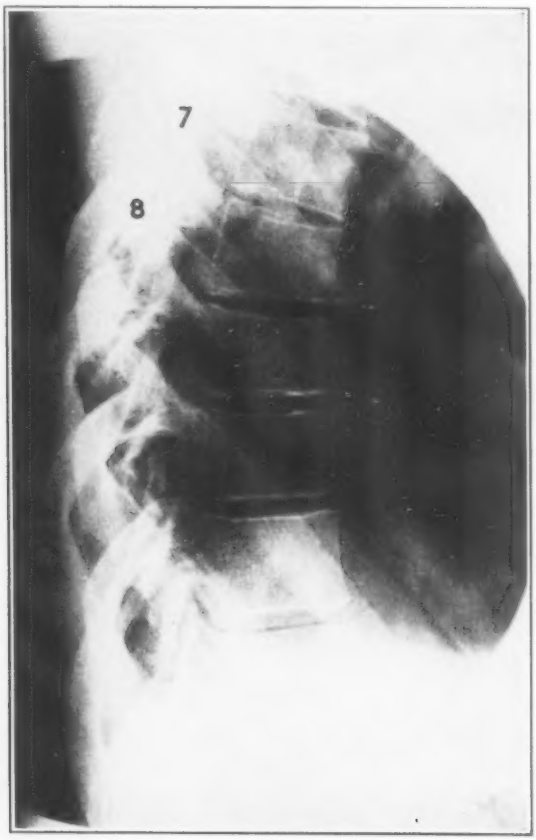


Fig. 5.—Table 3. Case 6. Irregular destructive changes along the anterior margin of D-7. Died. Coccidioidomycosis. (Case Report 3.)

COMMENT. Pathogenic fungi must be considered in the differential diagnosis of all infections involving bones and joints. Although neither clinical studies

nor roentgenographic examination can make an absolute distinction between a mycotic and a bacterial infection, there are certain distinguishing features that will aid in the differentiation. Mycotic joint and bone disease occurs as a part of a systemic infection. Dissemination or spread is by means of the blood stream with the possible exception of actinomycosis, in which case direct extension occurs. The lesions are usually multiple, widespread, and in general show a predilection for cancellous rather than tubular bone. In the case of cryptococcosis there is a tendency towards involvement of the bony prominences[1,3]. The roentgenographic appearance is that of an almost pure osteolytic process with little bone or periosteal reaction except, again, in occasional cases of actinomycosis. Sequestrae, if present, are usually small: a contrast with the usual reaction resulting from bacterial infection. When joints are involved, it is usually by direct extension from the initial bone lesion, and extensive damage occurs to the bone, cartilage and synovial membrane. Roentgen evidence of bone damage may exist for many months after skeletal pain and signs of systemic infection have disappeared. Tuberculous bone and joint lesions are most apt to be confused with mycotic infections, and

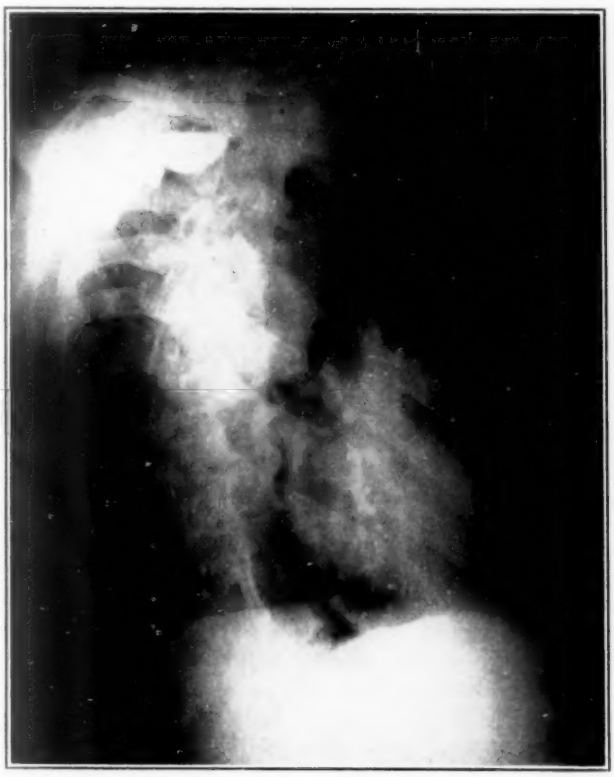

Fig. 6.—Table 3, Case 6. Iodized oil in sinus tract extending down to the lower cervical and upper dosal vertebrae. (Case Report 3.)

it may be almost impossible to differentiate the two. Solely from a roentgenographic standpoint, mycotic infection of the bone may be difficult to distinguish from multiple myeloma, certain cases of metastatic carcinoma, eosinophilic granuloma and other conditions. The clinical features of these varying diseases, however, should not offer real difficulty[1,2,4,6-8,15].

The failure to respond to the usual antibiotic and chemotherapeutic agents should arouse suspicion that the infection is not one resulting from the usual pathogenic bacteria. The diagnosis, however, can only be made by recovering the organism from the joint, bone, abscess cavity, sinus tract, skin, sputum, urine or spinal fluid.

The prognosis for certain of this group of diseases has improved, due to the introduction of the aromatic diamidines as a more effective treatment measure. Stilbamidine is unstable in solution, and has been found to be toxic for the trigeminal nerve; but 2-hydroxystilbamidine does not have these disadvantages and is equally effective. Blastomycosis, cryptococcosis (except of the central nervous system) and actinomycosis have proven to be the most effectively treated. The various sulfonamides and antibiotics have been effective in some cases of actinomycosis and nocardiosis. Iodides in various forms and quantities have formerly been the drugs used most extensively, and for the longest period of time. This drug has been effective to a limited degree in the treatment of blastomycosis, cryptococcosis, actinomycosis and nocardiosis. Otherwise, the management has been largely symptomatic, supportive or with the use of a wide variety of drugs and other treatment measures that enjoyed brief and unwarranted periods of popularity. To date, no treatment of value is available for coccidioidomycosis, histoplasmosis or central nervous system cryptococcosis[5,9-14].

**Summary.** 1. Eight cases of bone and joint disease were found in 25 cases of pathogenic mycotic infection observed in a period of 5 years. Five cases were due to the *Blastomyces dermatitidis*, 2 to the *Cryptococcus neoformans*, and one to the *Coccidioides immitis*. The number and character of the mycotic infections were not considered unusual for this area.

2. Bone lesions, as a rule, are osteolytic in nature, usually multiple, and involve cancellous rather than tubular bones. Joint involvement occurs by extension from the adjacent infected bone. In cases responding to treatment, roentgenographic evidence of bone damage may exist long after the systemic features and evidence of involvement of the other organs have disappeared.

3. The aromatic diamidines, particularly 2-hydroxystilbamidine, have been found to be effective in treating blastomycosis, actinomycosis and cryptococcosis (except in the central nervous system). Various sulfonamides and antibiotics have been helpful in some cases of actinomycosis and nocardiosis. Iodides in various forms are still being used in the treatment of a number of these diseases, but their use is limited. To date, no treatment of value is available for coccidioidomycosis, histoplasmosis or cryptococcosis of the central nervous system.

4. Diagnosis can be established only by recovering the organism from the joint, bone, abscess cavity, sinus tract, skin, sputum, urine or spinal fluid.

ACKNOWLEDGMENT: The authors wish to thank Dr. Virginia Thorpe for her aid in supplying the information and preparing the case reports on the cases of cryptococcosis.

REFERENCES

1. **Carter, R. A.:** Radiology, **23,** 1, 1934.
2. **Collins, V. P.:** Am. J. Roentgenol., **63,** 102, 1950.
3. **Conant, N. F., Smith, D. T., Baker, R. D., Callaway, J. L.,** and **Martin, D. S.:** Manual of Clinical Mycology, 2nd ed. Philadelphia: W. B. Saunders Co., 1954.
4. **Dykes, J., Segesman, J. K.,** and **Birsner, J. W.:** A.M.A. Am. J. Dis. Child., **85,** 34, 1953.
5. **Gordon, L. E., Smith, C. E., Tompkins, M.,** and **Saito, B. T.:** J. Lab. & Clin. Med., **43,** 942, 1954.
6. **Hall, R. H.,** and **Mendeloff, J.:** J. Bone and Joint Surg., **34–A,** 977, 1952.
7. **Leopold, S. S.:** Med. Clin. N. America, **37,** 1737, 1953.
8. **Miller, D.,** and **Birsner, J. W.:** Am. J. Roentgenol., **62,** 229, 1949.
9. **Miller, J. M., Schoenbach, E. B., Long, P. H., Shuttleworth, J. S.,** and **Snider, G. E.:** Antibiotics and Chemother., **2,** 444, 1952.
10. **Miller, J. M., Smith, G. W.,** and **Headley, W. H.:** Science, **118,** 31, 1953.
11. **Schoenbach, E. B., Miller, J. M.,** and **Long, P. H.:** Ann. Int. Med., **37,** 31, 1952.
12. **Snapper, I., Baker, L. A., Edidin, B. D.,** and **Kushner, D. S.:** Ibid., **43,** 271, 1955.
13. **Snapper, I.,** and **McVay, L. V., Jr.:** Am. J. Med., **15,** 603, 1953.
14. **Whitehill, M. R.,** and **Rawson, A. J.:** Virginia Med. Monthly, **81,** 591, 1954.
15. **Wiener, M. F.:** A.M.A. Arch. Int. Med., **87,** 713, 1951.

## SUMMARIO IN INTERLINGUA

### Morbo de Osso e Articulation Debite a Infection Mycotic

1. Octo casos de morbo de osso e articulation esseva trovate inter le 25 casos de infection mycotic observate durante un periodo de 5 annos. Cinque casos esseva debite a *Blastomyces dermatitidis,* 2 a *Cryptococcus neoformans,* e 1 a *Coccidioides immitis.* Le numero e le character del infectiones mycotic non esseva considerate como extraordinari pro iste region (Richmond, Virginia).

2. Lesiones ossee es generalmente de natura osteolytic. Illos es usualmente multiple e affice ossos cancellos plus tosto que tubular. Le affection del articulationes occurre per extension ab le inficite osso adjacente. In casos que responde al therapia, le signos roentgenographic del lesion ossee pote persister longe post que le tractos systemic e le symptomas del involvimento del altere organos ha disparite.

3. Le diamidinas aromatic, specialmente 2-hydroxystilbamidina, se ha provate efficace in tractar blastomycosis, actinomycosis, e cryptococcosis (excepte in le systema nervose central). Varie sulfonamidos e antibioticos ha essite de adjuta in certe casos de actinomycosis e nocardiosis. Iodidos in varie formas es ancora in uso in le tractamento de un numero de iste morbos, sed iste typo therapeutic es limitate. Al tempore presente nulle tractamento de valor es disponibile pro coccidioidomycosis, hystoplasmosis, o cryptococcosis del systema nervose central.

4. Le diagnose pote esser establite solmente per identificar le organismo responsabile in osso, articulation, abscesso, tracto sinusal, pelle, sputo, urina, o fluido spinal.

# FURTHER OBSERVATIONS ON THE CARDIOVASCULAR EFFECTS OF SODIUM LACTATE:* EFFECT IN NORMAL SUBJECTS AND IN VARIOUS ARRHYTHMIAS**

By Samuel Bellet, M.D.
DIRECTOR, DIVISION OF CARDIOLOGY, PHILADELPHIA GENERAL HOSPITAL; DIRECTOR, DIVISION OF CARDIOVASCULAR DISEASE, GRADUATE HOSPITAL, UNIVERSITY OF PENNSYLVANIA

Fred Wasserman, M.D.
FELLOW OF THE HEART ASSOCIATION OF SOUTHEASTERN PENNSYLVANIA, GRADUATE HOSPITAL, UNIVERSITY OF PENNSYLVANIA

AND

Jerome I. Brody, M.D.
RESIDENT IN CARDIOLOGY, PHILADELPHIA GENERAL HOSPITAL

(From the Philadelphia General Hospital, the Graduate Hospital of the University of Pennsylvania and the Robinette Foundation of the University of Pennsylvania, Philadelphia, Pennsylvania)

Recent studies in this laboratory have shown the marked effect of molar sodium lactate on increasing the rhythmicity of the cardiac pacemakers in the presence of slow heart rates. The drugs available for increasing the heart rate in the presence of the slow sinus or nodal rhythm consist of vagolytic[3,11] or sympathomimetic drugs[3,9,12]. For a slow idioventricular rhythm, the latter are usually employed (epinephrine, ephedrine, and others). Occasionally, drugs such as barium chloride which act by increasing cardiac irritability have been employed[8]. However, their use has been infrequent because of a tendency to produce serious arrhythmias. The effects of sodium lactate appear to be based on an entirely new principle which, as far as we know, has not previously been described in the intact animal or the human subject.

In a previous communication[5], we discussed the ability of this solution to increase the idioventricular rate of complete A–V heart block and to restore ventricular beating in the presence of cardiac arrest associated with Stokes-Adams seizures and in the terminal or dying heart. The object of this report is to present further studies relative to the effect of this solution in various cardiac disturbances accompanied by slow heart rates and also to present its effect in the normal subject. It was hoped that this study would help to determine more definitively the mode of action, scope of effect and the range of conditions in which sodium lactate administration might be efficacious. The presence of any untoward effects was also studied.

**Methods and Materials.** The effect of intravenous molar sodium lactate was studied in 5 normal patients and in 27 patients with

*The molar lactate used in these studies was kindly supplied by Eli Lilly and Co., Indianapolis, Indiana.

**This work was supported by a grant from the Foundation for Cardiovascular Research and was aided by the U. S. Public Health Service Grant H141 (C6).

cardiovascular disturbances, including partial A–V heart block, sinus bradycardia, hypersensitivity of the carotid sinus and in the presence of premature beats. In addition, the effect on the widened QRS complex, T wave and QT segment was noted (Table 1). These studies were correlated with the various electrolyte and blood chemistry alterations produced by the infusion.

Serum sodium and potassium were determined by the flame photometric method using lithium as the internal standard on the Process Flame Photometer, serum calcium by the method of Clark and Collip[7], serum chloride by the method of Wilson and Bell[16], $CO_2$-combining power by the method of Van Slyke and Cullen[15], and serum lactate by the method of Barker and Summerson[2].

TABLE 1.

| *Types of Cases and Rhythm* | *No. of Cases* | *Amount of Sodium Lactate Administration and Time Involved* |
|---|---|---|
| Normal subjects | 5 | 100 to 200 ml. in 10 to 15 minutes |
| Myocardial abnormality with normal sinus rhythm | 4 | 100 to 200 ml. molar lactate in 9 to 20 minutes, 1000 ml. half-molar lactate in 4 hours |
| Partial A-V heart block (5 with NSR, 1 with atrial fibrillation) | 6 | 100 to 140 ml. in 10 to 30 minutes |
| Sinus bradycardia | 3* | 100 to 150 ml. in 10 minutes |
| Carotid sinus hypersensitivity | 4 | 120 ml. in 10 to 15 minutes |
| QRS widening | 8* | (*a*) 90 to 150 ml. in 10 to 15 minutes<br>(*b*) 900 ml. in 5 hours |
| Extrasystoles (atrial and ventricular) | 4 | 100 to 200 ml. in 9 to 20 minutes |
| | 34 | |

* Includes one case of partial A–V heart block

Blood pH was determined on the Beckman pH meter using the hypodermic glass electrode under anaerobic conditions and temperature was corrected to 38° C. body temperature.

Following clinical examination, a control electrocardiogram, a pH and the following electrolytes and blood chemistries were obtained: sodium, potassium, calcium, chloride, lactic acid and $CO_2$-combining power. Molar sodium lactate in a dose of 100 ml. to 200 ml. was infused intravenously over a period of 10 or 15 minutes. Almost continuous electrocardiograms were taken and frequent electrolyte studies were obtained during the infusion and for several hours thereafter until the electrocardiogram returned to normal. The maximum effect was usually observed toward the end of the infusion or a few minutes thereafter. Where the effect tended to persist, the observation was continued until the electrocardiogram returned to its normal state.

**Results.** EFFECT IN NORMAL SUBJECTS. Molar sodium lactate solution was administered in 5 normal subjects ranging from 19 to 27 years of age. The limb, unipolar and precordial leads were taken during the control period. Following this, 100, 120, 140, 160 and 200 ml. of molar sodium lactate respectively, was administered over a 10- to 15-minute period. The tracings were repeated at the point of maximum increase in pH which occurred usually within 10 to 20 minutes after the cessation of the infusion. There was no significant change in the heart rate or in the electrocardiogram during the period of observation. The alterations in blood pH, electrolytes and chemistry are noted in Fig. 1.

COMMENT. No clinical effects were observed following the administration of sodium lactate to these normal subjects. There was no significant change in the pulse rate, blood pressure or the electrocardiogram. However, significant alterations in the electrolytes, pH and blood chemistries were observed as noted in Fig. 1.

ABNORMAL CLINICAL STATES WITH NORMAL SINUS RHYTHM AND NORMAL HEART RATES. For many years, one-sixth molar sodium lactate, and, more re-

cently, molar sodium lactate, have been used for the treatment of acidosis of various etiologies[10,13]. Although many of these patients manifested evidence of myocardial abnormalities, some of which were of a rather severe grade, this solution was well tolerated with relatively few side effects. It was considered worthwhile, therefore, to correlate electrocardiographic with electrolyte and blood chemical alterations in such a group.

Four patients with severe myocardial damage and normal heart rates were given varying amounts of molar sodium lactate. A 44-year-old male with malignant hypertension, marked congestive heart failure, uremia and acidosis was given 120 ml. of sodium lactate in 20 minutes; a transient bigeminal rhythm was observed 10 minutes after completion of the lactate infusion. This persisted for about one minute. A 65-year-old man with apparent hyperpotassemia and severe acidosis was given 200 ml. of molar sodium lactate over a period of 15 minutes and 1000 ml. of half molar lactate over a 4-hour period; although this patient was given large doses of sodium lactate because of a laboratory error indicating hyperkalemia, the only electrocardiographic effects noted after the lactate were a slight prolongation of the QT interval and further depression of the ST segments beyond that seen in the control tracing. A 58-year-old male with hypertensive and rheumatic heart disease

| Time mins | $Na^+$ meq/ | $K^+$ meq/ | pH units | $CO_2$cp vol % | $Ca^{++}$ mg % | Lactic acid |
|---|---|---|---|---|---|---|
| 0 | 1421 | 4.49 | 7.36 | 54 | 9.6 | 1176 |
| 15 | 1452 | 4.10 | 7.40 | 54 | 9.4 | 4940 |
| 30 | 1472 | 4.10 | 7.47 | 58 | 9.4 | 4360 |
| 45 | 1452 | 3.97 | 7.41 | 54 | 9.3 | 3007 |
| 60 | 1421 | 4.03 | 7.42 | 52 | 9.3 | 2768 |
| 75 | 1411 | 3.89 | 7.42 | 52 | 9.4 | 2329 |
| 90 | 1411 | 4.00 | 7.42 | 52 | 9.4 | 1500 |

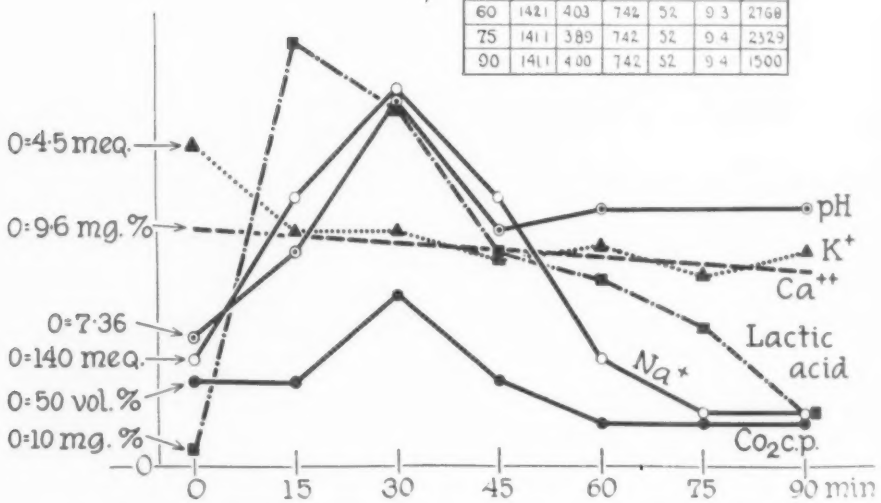


Fig. 1.—The graph represents the typical electrolyte and blood chemistry occurring when 160 ml. of molar sodium lactate was administered in 15 minutes to a healthy, 19-year-old white female. The accompanying table represents the exact figures obtained from which the graph was plotted.

and digitalis intoxication with multifocal premature beats was given 100 ml. of molar sodium lactate over a period of 9 minutes. A transient increase in the premature beats of multifocal origin was observed in this patient at the height of the lactate effect. Finally, a 59-year-old male diabetic with uremia, acidosis and hyperpotassemia was given 120 ml. of molar sodium lactate over a period of 15 minutes. The only finding was a slight depression of the RS–T segments following the lactate infusion.

COMMENT. Our experience with this group and with others of this category (not mentioned in this paper) with serious myocardial damage would indicate that the solution may be given in relatively large doses without severe untoward effects. Occasionally, extrasystoles are observed which may be a manifestation of an early toxic effect and which might possibly become more severe if extremely large doses were to be used. Doses of 100 to 200 ml. administered within a period of 10 to 15 minutes are usually well tolerated. These results are similar to the findings previously reported. Administration of larger doses should be controlled by the electrocardiogram and serum electrolyte determinations.

EFFECT IN PARTIAL A–V HEART BLOCK. The effect of 100 to 120 ml. of molar sodium lactate administered over a period of about 10 minutes was studied in 6 cases of partial A–V heart block. These included subjects with 2:1 A–V heart block, (2 cases); 2:1 A–V heart block with dropped beats, (1 case); partial A–V heart block with sinus bradycardia, (1 case); simple PR prolongation, (1 case); and one patient with atrial fibrillation receiving digitalis.

**Case Reports.** CASE 1. E.N., a 43-year-old white man was admitted to the Philadelphia General Hospital with a history of having had a coronary occlusion about one year before, after which he experienced anginal seizures and occasional syncopal attacks. Examination revealed the heart to be normal in size; no murmurs were audible. The blood pressure was 140/70. The rhythm was irregular with a slow heart rate averaging 38 per minute. The electrocardiogram showed a partial A–V heart block with frequent dropped beats (Fig. 2*A*). On January 1, 1955, 120 ml. of molar sodium lactate was infused over a period of 15 minutes. The control tracing showed an average rate of 35 per minute (counted over a period of 2 minutes). After 90 ml. of the solution had been given, the heart rate increased to 49 per minute (Fig. 2*B*) and the dropped beats almost entirely disappeared. The PR intervals, which in the control (short cycle) were 0.40 second, were shortened to 0.32 second. There was no demonstrable effect on the blood pressure. Forty-five minutes after administration of the sodium lactate, the tracing had returned to practically the control figure (Fig. 2*C*). The serum electrolytes and blood chemistries (sodium, potassium, calcium and $CO_2$-combining power) determined before and 45 minutes after infusion, were within normal range.

CASE 2. C.S., an 81-year-old white man, was admitted to the Philadelphia General Hospital on December 16, 1954, with a diagnosis of arteriosclerotic heart disease, aortic stenosis and a slight degree of aortic insufficiency. The heart was top normal in size and the blood pressure was 160/60. There was no evidence of congestive failure. The control electrocardiogram, on January 3, 1955, showed a 2:1 A–V heart block (Fig. 3*A*). Following the administration of 120 ml. of molar sodium lactate in a period of 10 minutes, the ventricular rate increased from 38 to 50 and the atrial rate increased from 75 to 100 per minute. The 2:1 A–V heart block persisted (Fig. 3*E*). At the height of the effect, the T wave became inverted (Lead II) and the QT interval became prolonged. The terminal inversion also probably contained an inverted U wave (Fig. 3*C*). This change was transient and lasted about two minutes (Table 2). There was no alteration in blood pressure, and the serum electrolytes before and 45 minutes after injection, showed no significant change.

COMMENT. Administration of the sodium lactate resulted in a significant increase in the atrial and ventricular rates. However, other significant

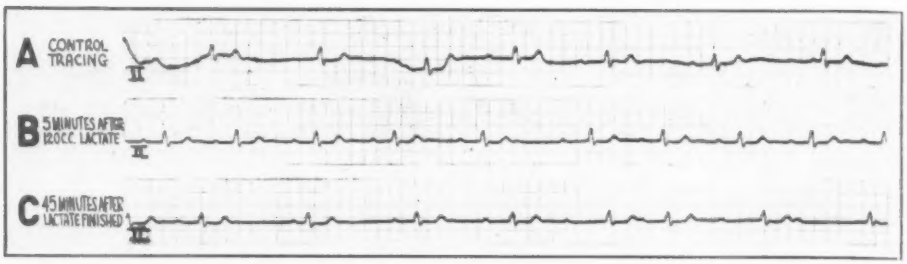


Fig. 2.—E.N., a 43-year-old white male. *A*, Control (Lead II) tracing. Ventricular rate averages 35 per minute. In the conducted beats, the PR interval measures 0.40 second. *B*, Five minutes after 120 ml. of molar sodium lactate had been given (over a period of about 15 minutes). The ventricular rate has increased to 49 per minute. The PR interval (in the short cycles) has been shortened to 0.32 second. *C*, Forty-five minutes after the sodium lactate had been given, the ventricular rate is again 35 per minute and the PR interval now measures 0.44 second.

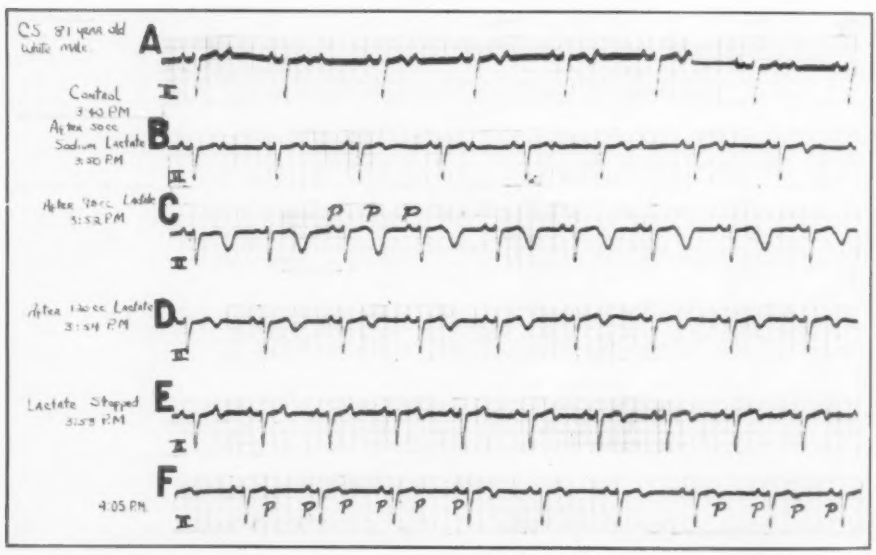


Fig. 3.—C.S., an 81-year-old white male with partial A–V heart block. *A*, Control tracing (Lead II) shows an atrial rate of 74 per minute and a ventricular rate of 37 per minute. *B*, At 3:50 P.M., following 50 ml. of molar sodium lactate given in 5 minutes, the atrial rate is 78 per minute and the ventricular rate is 39 per minute. *C*, At 3:52 P.M., 90 ml. of sodium lactate had been infused over a period of 7 minutes. The atrial rate is 88 per minute and the ventricular rate is 44 per minute. Note the deep inversion of the T and U waves and the prolongation of ventricular repolarization (ST segment). *D*, After 14 minutes, during which 120 ml. of sodium lactate was infused, the atrial rate is 88 per minute and the ventricular rate is 44 per minute. There is less inversion of the T and U waves. *E*, At 3.58 P.M., 4 minutes after the lactate had been stopped, the atrial rate is 100 per minute and the ventricular rate is 50 per minute. The T and U waves are now of a more normal configuration. *F*, At 4:05 P.M., 11 minutes after the lactate had been discontinued, the atrial rate has decreased to 90 per minute and the ventricular rate to 45 per minute. The T and U waves resemble the control configurations. The P wave following the T wave presents a different configuration from that preceding the QRS, suggesting that it arises from a different focus in the atrium.

changes observed were the inverted U waves with prolongation of the period of ventricular repolarization (ST segments) at the height of the effect. This finding would indicate that a profound, although transient, alteration had occurred in the electrolytes within the heart muscle or the extracellular fluid bathing the cells. These electrocardiographic changes are similar to those observed with a low serum potassium associated with metabolic alkalosis[4].

CASE 3. M.B., a 48-year-old white woman, admitted to the Graduate Hospital of the University of Pennsylvania was diagnosed as having essential hypertension with cardiac en-

TABLE 2.—EFFECT OF MOLAR SODIUM LACTATE ON THE ELECTROCARDIOGRAM IN CASE 2

| | *Time* | *No. of ml.* | *Atrial Rate* | *Ventricular Rate* | *T Waves and QT Intervals* |
|---|---|---|---|---|---|
| 1. Control | 3:40 P.M. | .. | 74 | 37 | Upright T with terminal dip |
| 2. Molar sodium lactate started | 3:45 P.M. | .. | 74 | 37 | No change |
| 3. | 3:50 P.M. | 50 | 78 | 39 | No change |
| 4. Molar sodium lactate stopped | 3:52 P.M. | 120 | 78 | 44 | Inverted T wave (TU wave) |
| 5. | 3:58 P.M. | .. | 100 | 50 | T wave upright |
| 6. | 4:02 P.M. | .. | 102 | 51 | |
| 7. | 4:05 P.M. | .. | 90 | 45 | P waves after T waves arise from different focus |
| 8. | 4:10 P.M. | .. | 90 | 45 | |
| 9. | 4:15 P.M. | .. | 90 | 45 | |
| 10. | 6:00 P.M. | .. | 90 | 45 | |

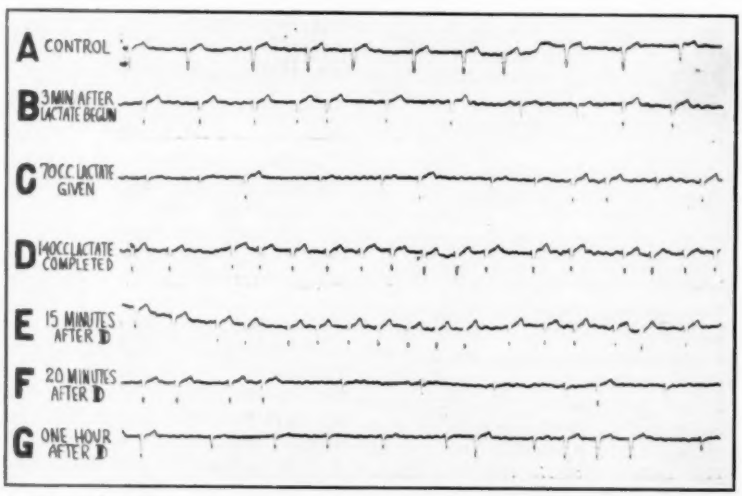
A CONTROL
B 3 MIN. AFTER LACTATE BEGUN
C 70CC LACTATE GIVEN
D 140CC LACTATE COMPLETED
E 15 MINUTES AFTER D
F 20 MINUTES AFTER D
G ONE HOUR AFTER D

Fig. 4.—*A*, Control. Note presence of atrial fibrillation with a ventricular rate of approximately 44 per minute. *B*, Three minutes after starting lactate. Note the occurrence of occasional QRS complexes the width of which is narrower than the control. *C*, Note increase in the frequency of the narrowed QRS complexes. *D*, Note increase of ventricular rate to approximately 80 per minute. *E*, Fifteen minutes after lactate stopped. Note ventricular rate of about 80 per minute. *F*, Twenty minutes after stopping lactate, there is slowing of the ventricular rate and frequent narrowed QRS complexes are observed. *G*, One hour after lactate stopped. Note that QRS complexes following long cycles are narrowed and those following short cycles are widened. (Those following long cycles in strip *A* were all widened.)

largement and left ventricular hypertrophy. There was no evidence of congestive failure. The control electrocardiogram showed a mild sinus arrhythmia with a partial A–V heart block (PR interval, 0.22 second). Following the administration of 100 ml. of molar sodium lactate in 10 minutes, the PR interval decreased slightly to 0.20 second without any change in the heart rate.

CASE 4. N.I., a 78-year-old Negro male was admitted to the Philadelphia General Hospital on February 7, 1955, with the diagnosis of arteriosclerotic cardiovascular disease and congestive heart failure. Examination revealed distention of the neck veins, enlargement of the heart to the left, and an irregular rhythm due to atrial fibrillation. The blood pressure was 150/90. The lungs were clear. The liver was palpable 4 finger breadths below the right costal margin and there was a 2+ pitting edema of the ankles. The patient improved markedly on a regimen of bed rest, digitalis, mercurial diuretics and a low salt diet. On February 28, 1955, when this patient's ventricular rate was 44 per minute, he was given 140 ml. of molar sodium lactate over a 30-minute period. The solution increased the ventricular rate from 44 to 80 per minute and resulted in a narrowing of the QRS width (Fig. 4).

CASE 5. N.C., an 84-year-old Negro male was admitted to the Graduate Hospital of the University of Pennsylvania with digitalis intoxication. On April 15, 1955, the electrocardiogram showed varying grades of partial A–V heart block (2:1 and prolonged PR interval) and an average ventricular rate of 45 per minute. He was given 100 ml. of molar sodium lactate over a period of 15 minutes. At the termination of the infusion, and for approximately 30 minutes thereafter, 1:1 A–V conduction with simple PR prolongation was the predominant rhythm. The ventricular rate increased to 80 per minute. One hour after completing the infusion, a 2:1 A–V heart block alternating with a first degree A–V heart block had returned. Subsequently, the ventricular rate gradually slowed to the control level.

The sixth case is discussed on this page under Sinus Bradycardia.

SUMMARY OF EFFECTS. Of the 6 patients with partial A–V heart block to whom molar sodium lactate was administered, the case with atrial fibrillation developed a marked increase in the ventricular rate (from 44 to 80 per minute), 2 developed a slight increase in the ventricular rate (from 35 to 49 per minute and from 38 to 50 per minute, respectively), 2 others showed no demonstrable change. Of the 5 with sinus rhythm, the ventricular rate was increased in 2 patients (from 35 to 45 and from 74 to 102 per minute) and was unchanged in 3 others. The PR interval was decreased in 2 of these patients. In Case 2, the atrial and ventricular rate increased without changing the degree of the A–V heart block. The QRS complexes were narrowed in one of these patients (Case 3) and in another, (Case 2), the QT intervals were lengthened and T waves became deeply inverted at the height of the effect (Fig. 3C).

It is difficult to explain the marked variation in the effects observed following the molar lactate administration. Its capacity to increase the heart rate apparently depends upon the dose and rapidity with which it is given, and this may be modified by the inherent pathology or functional alteration in the heart prior to lactate administration.

EFFECT IN SINUS BRADYCARDIA. The effect of molar sodium lactate was studied in 3 cases of sinus bradycardia in patients aged 59, 61 and 69 years of age, respectively.

**Case Report.** CASE 1. A.B., a 69-year-old white male was admitted to the Graduate Hospital of the University of Pennsylvania with the diagnosis of hypertensive and arteriosclerotic heart disease and cardiac enlargement. In addition, he experienced occasional periods of unconsciousness, probably the result of the cardio-inhibitory type of carotid sinus syncope. The serum electrolytes (sodium, chloride and potassium) and the blood urea nitrogen were within the normal range. The control electrocardiogram (Fig. 5) showed a slow sinus rate which ranged from 25 to 40 per minute, the PR interval measured 0.40 second and the QRS complexes were slightly widened in the terminal portion. Following the administration of 100 ml. of molar

sodium lactate in 10 minutes, the ventricular rate became regular at 45 per minute, the sinus pauses were abolished but the PR intervals were unaffected (Fig. 5*B*).

In two other cases of sinus bradycardia, aged 59 and 61, respectively, the ventricular rate increased from 42 to 51 and from 30 to 64 per minute, as a result of the administration of 150 ml. of molar sodium lactate within a period of 10 minutes.

EFFECT ON CAROTID SINUS HYPERSENSITIVITY. The effect of molar sodium lactate on carotid sinus hypersensitivity was studied in 4 patients. These subjects, aged 58, 63, 75 and 82 respectively, developed marked sinus slowing and ventricular escape in the control tracing following slight pressure high over the carotid artery. Following this observation, 120 ml. of the molar sodium lactate was given intravenously over a 10-minute period. Carotid sinus pressure was again applied after half of the lactate had been administered, immediately following the infusion and at intervals of 15 minutes and 30 minutes following its cessation. These studies failed to reveal a significant alteration of the carotid sinus sensitivity following sodium lactate administration.

EFFECT IN EXTRASYSTOLES. The relation between sodium lactate and the production (or abolition) of extrasystoles is illustrated in the following case reports.

**Case Reports.** CASE 1. A.B., a 44-year-old man was admitted to the Philadelphia General Hospital on February 4, 1955, with malignant hypertension, uremia and marked congestive heart failure. The heart was greatly enlarged; a grade IV hypertensive retinopathy, a bilateral pleural effusion, ascites and +3 peripheral edema were present. On February 7, the $CO_2$ was 4.5 vol. %, the BUN was 120 mg. per 100 ml., the serum chlorides were 102.9, the sodium was 138 and the potassium 4.9 mEq./L. On February 8, 1955, the patient was given an infusion of 120 ml. of molar sodium lactate over a 20-minute period. Ten minutes after the infusion, a bigeminal rhythm was noted which persisted for about one minute and corresponded to the maximal rise in pH from 7.33 to 7.39.

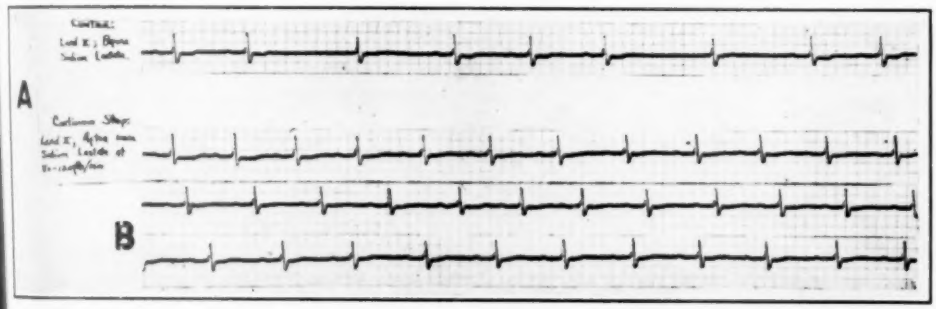


Fig. 5.—Effect of sodium lactate in bradycardia with periods of nodal escape. *A*, Control, before sodium lactate (Lead II). Note sinus bradycardia with slight irregularity due to sinus arrhythmia and periods of nodal escape. The ventricular rate ranged from 25 to 45 per minute and the PR interval is 0.40 second. *B*, After 100 ml. molar sodium lactate given at a rate of 80 to 120 drops per minute. Note the increase in ventricular rate to 45 per minute, abolition of the sinus arrhythmia and episodes of ventricular escape.

CASE 2. R.G., a 58-year-old white male, was admitted to the Graduate Hospital of the University of Pennsylvania on January 8, 1955, because of weakness, dyspnea and intractable hiccoughs of 48 hours' duration. The diagnosis was hypertensive and rheumatic heart disease with cardiac enlargement, left ventricular hypertrophy, aortic insufficiency,

mitral insufficiency and digitalis toxicity. An electrocardiogram on admission showed frequent ventricular extrasystoles with a coupled rhythm. One hundred milliliters of molar sodium lactate was infused over a period of 9 minutes. At the height of the lactate effect, there occurred an increase in the number of premature beats of multifocal origin.

CASE 3. F.S., an 87-year-old white man, was admitted to the Philadelphia General Hospital because of arteriosclerotic heart disease with aortic stenosis. The heart was normal in size and the electrocardiogram showed atrial fibrillation with complete A–V heart block. The ventricular rate was 39 per minute. One hundred milliliters of molar sodium lactate was administered to the patient over a period of 10 minutes. The ventricular rate increased to 48 per minute at the end of the infusion which apparently represented the peak effect. Two minutes after completion of the infusion, a transient period of coupling, which lasted about one minute, was noted.

CASE 4. C.C., a 38-year-old Negro male, was admitted to the Graduate Hospital of the University of Pennsylvania on February 8, 1955, because of pain due to a rectal fissure. Examination on admission revealed no evidence of cardiac abnormality except for a bigeminal rhythm. After a period of study, this arrhythmia was considered to be of functional origin rather than the result of myocardial disease. On February 11, 1955, the patient was given 160 ml. of molar sodium lactate over a period of about 10 to 15 minutes. Immediately after completion of the infusion, the ventricular extrasystoles became much less frequent and then disappeared entirely (Fig. 6*C*). Normal sinus rhythm continued for about 1½ hours without additional sodium lactate administration. After this period, the premature beats gradually returned. Serum electrolytes and blood chemistries (sodium, potassium, chlorides and $CO_2$-combining power) were normal in the control and showed no significant change 30 minutes after sodium lactate administration.

Fig. 6.—Effect of molar sodium lactate on bigeminal rhythm in a normal heart. *A*, Note regular coupled ventricular extrasystoles following each normal beat. *B*, One minute after 160 ml. sodium lactate intravenously in 15 minutes, note only occasional extrasystoles. *C*, Two and one-half minutes after lactate, note normal sinus rhythm with ventricular rate of 75 per minute. *D*, Five minutes after lactate, note occasional ventricular extrasystoles. *E*, Ninety minutes after lactate, normal sinus rhythm with beginning return of coupled extrasystoles at the end of the strip.

COMMENT. Ventricular extrasystoles were observed in 2 cases as a transient

phenomenon lasting about one minute during the height of the sodium lactate effect. The frequency of ventricular extrasystoles due to digitalis toxicity was increased in a third. These ectopic beats were present in patients with severe heart damage associated with marked congestive failure. In a fourth patient with continuous coupled ventricular extrasystoles of functional origin, normal rhythm was restored for a period of 1½ hours following the administration of molar sodium lactate.

EFFECT ON WIDENED QRS COMPLEXES. Conspicuous narrowing of widened ventricular complexes was observed in 8 cases of our series. This change was observed in the following categories: complete A–V heart block (4 cases); partial A–V heart block (1 case); terminal cardiac arrest (2 cases); and intermittent right bundle branch block (1 case). In the patients with complete A–V heart block, QRS narrowing was particularly apt to occur coincident with speeding of the rate[5] but narrowing was observed occasionally without a significant change in the ventricular rate (Fig. 7*B–C*). When lactate was administered to asymptomatic patients with complete or partial A–V heart block, a narrowing of the QRS occurred in 3 subjects. These changes were transient lasting for a few cycles or a few minutes following the infusion of 90 to 150 ml. of lactate

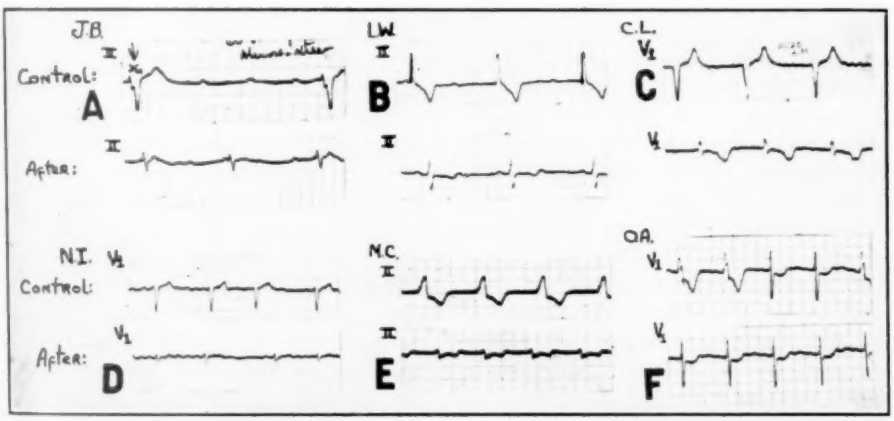


Fig. 7.—Effect of molar sodium lactate in narrowing widened QRS complexes. The top strip in each case represents widened QRS complexes in the control tracing. The lower strip represents the same lead following administration of molar sodium lactate. *A*, From patient with complete A–V heart block and hyperpotassemia (serum potassium 7.3 mEq./L.). After administration of sodium lactate, note increase from 18 per minute to 38 per minute and marked narrowing of QRS complexes. *B*, Patient with complete A–V heart block, occasional conducted beats were observed. After infusion, normal A–V conduction was present with slight narrowing of the QRS complex. *C*, Complete A–V heart block with atrial fibrillation. Ventricular rate: 42 per minute. After molar sodium lactate, note speeding of the ventricular rate, narrowing of the QRS complexes. The T waves are now inverted, and the ST segments prolonged. *D*, Partial A–V heart block with atrial fibrillation. Following infusion, note narrowing of QRS complexes. *E*, From a patient with terminal cardiac arrest: Upper strip, Lead II, shows widened QRS complexes measuring 0.16 second followed by inverted T waves. After lactate injection, note marked narrowing of the ventricular complexes and change in the T wave. *F*, From a patient with intermittent right bundle branch block. Note slightly widened ventricular complexes followed by QRS complexes with normal width. Following molar lactate, the widened complexes have entirely disappeared.

solution. However, lactate was also administered to patients with complete heart block occurring in the presence of shock or idioventricular rhythm, or both, associated with cardiac arrest. In this instance, the lactate solution was administered in larger doses over a period of 5 hours and the QRS changes persisted for several hours. However, a reversion to the widened QRS complexes occurred as the infusion was slowed or stopped and the narrowing returned with resumption of the infusion. In 2 cases, the narrowing persisted after the injection was stopped (Cases 1 and 4)[5]. The decrease in QRS width was also often coincident with the improvement in the clinical state. In 2 patients, widened QRS complexes were associated with hyperpotassemia. In both of these, marked narrowing was observed within a few minutes after starting the lactate infusion. Conspicuous decrease in QRS width was observed in 2 patients with terminal cardiac arrest. The narrowing of the QRS complexes was often accompanied by ST and T wave changes as noted below.

EFFECT ON BLOOD PRESSURE. In normal subjects, 100 to 200 ml. of sodium lactate administered over a 10-minute period had no significant effect on the blood pressure. The administration of the solution over similar periods of time to normal dogs (5 ml. per kilo) also produced no change in the blood pressure[6]. In the patients with partial A–V heart block where slight changes in ventricular rates were noted, no significant alteration in blood pressure was observed. In 3 compensated cases of complete A–V heart block, there was no significant change in blood pressure. In cases where cardiac arrest occurred during Stokes-Adams attacks, the blood pressure was restored to a relatively normal value as the heart beat was restored. In a case of terminal cardiac arrest, although the blood pressure was increased, it did not attain a normal value (reference 5, Case 2). In a subject with a complete A–V heart block and a ventricular rate of 15 per minute, in whom the blood pressure was initially unobtainable, following the sodium lactate administration, the blood pressure increased to 120 to 140 systolic as the heart rate speeded (reference 5, Case 4). It should be emphasized, however, that the administration of molar sodium lactate in the terminal phase (beyond the critical period) although often efficacious in restoring the heart beat (as evidenced by the electrocardiogram) does not necessarily produce a rise in blood pressure or result in resuscitation. This has also been found to be true in the terminal phase of asphyxia in the dog[6].

**Discussion.** METHODS OF ADMINISTRATION AND DOSAGE. In a previous communication[5], we discussed the administration of varying doses of molar sodium lactate depending upon the individual state of the patient. The rapidity of administration and the dosage that are safe have, as yet, not been definitely determined. In the cases of this series, when lactate was given to patients with normal hearts, the dosage ranged from 100 ml. to about 200 ml. administered over a period of 10 to 20 minutes. For routine therapy or when larger doses are given, 0.125% of calcium chloride should be given to prevent tetany[10]. In patients with cardiac arrest, and in the terminal state, doses of 15 ml. to 250 ml. were required over a short period of time to restore cardiac beating. The rapidity of the injection depended upon the urgency for restoring the heart beat. Generally, 5 to 7 ml. per kg. of molar solution* may be administered over a period of ½ hour to 1 hour. About 5

*Each 100 ml. of the solution as supplied contains sodium lactate 11.2 gm. representing 11.2% (W/V). In terms of potential alkali, it equals 8.4 gm. (approximately 13 gm.) sodium bicarbonate.

to 7 ml. per kilo has been given to normal subjects in a period of 30 minutes to one hour without untoward effect[10]. However, in patients with serious heart damage, cardiac enlargement and congestive failure, small doses should be used. The electrocardiogram appears to be a good guide for detecting immediate untoward effects in the form of extrasystoles or marked T wave changes. The majority of patients, even those with diseased hearts, tolerate the solution without serious toxic effects. Doses up to 500 ml. of the molar lactate have been given over a period of 1 to 2 hours to maintain an adequate heart rhythm without untoward effect. We have given 200 ml. of molar sodium lactate in 15 minutes followed by 1000 ml. of half-molar in 4 hours with resulting alkalosis without untoward effect.

FATE OF THE SODIUM LACTATE AND ELECTROLYTE ALTERATIONS. When given in the doses of 5 to 7 ml. per kilo in about one-half hour, the sodium lactate is completely metabolized in a period of 1 to 2 hours by normal subjects[10]. A portion of the lactate radical is oxidized and the remainder converted into glycogen. The lactic acid concentration increases in the blood and reaches a concentration of 120 mg. per 100 ml. in about one hour after the injection of 220 ml. of molar sodium lactate and usually returns to a normal level within 1 to 2 hours after the injection is started. In our cases, with a dosage of from 150 to 200 ml. of molar lactate administered in a period of 10 to 15 minutes, the concentration increased from 12 to 50 mg. 15 minutes after infusion was begun. This gradually returned to normal within 90 minutes. Abramson *et al.*[1] (1927) pointed out that the injected lactate acts as an easily oxidizable substrate which replaces other foodstuffs in metabolism.

When given 160 ml. of molar sodium lactate in a period of 15 minutes to normal subjects, the following was the general pattern of electrolyte alterations observed: the pH increases from 0.05 to 0.10 above the control noted. The maximum effect was observed approximately 20 minutes after cessation of injection. This elevation tended to be maintained for about ½ hour and then declined slowly reaching the control value in about 1 to 1½ hours after injection; the serum sodium was increased 3 to 8 mEq./L. and often no significant changes were observed. The potassium usually dropped from 0.4 to 0.7 mEq./L. reaching its maximum in about 1 hour and tended to return to normal at about the end of 1½ to 2 hours. Occasionally, no significant change was observed. The calcium was decreased from 1.0 to 1.5 mg. per 100 ml. or remained unchanged. The $CO_2$-combining power increased 4 to 5 vol. %. The graph (Fig. 1) illustrates the typical changes in the normal subject.

The sodium ion, liberated through the oxidation of lactate or its conversion into glycogen, is transported to the kidney for excretion largely as a bicarbonate salt. There exists, therefore, a state of alkalosis of the base bicarbonate type for 1 to 2 hours after injection with commensurate decrease in the hydrogen ion concentration of the blood. Within 4 hours, more than half of the injected sodium is excreted. The sodium increase, however, is less than might be anticipated from the amount injected because of the expansion of the extracellular space, elimination in the urine and, to some degree, because of its movement intracellularly[14]. The decrease in serum potassium is largely due to the increased excretion in the urine and expansion of the extracellular space. The fall in serum chloride is largely the result of the expansion of the extracellular space.

This and the associated mild alkalosis probably also explain the decrease in serum calcium. The electrolyte changes are somewhat similar to, but occur more slowly than those resulting from administration of hypertonic sodium bicarbonate[14]. As Singer *et al.*[14] have shown, the amount of excess buffer base in the blood following infusion was the sum of the amount reflected in the rise of plasma volume, in the red cells, and the substitution of other buffer anions for some of the bicarbonate as part of the increase in pH.

CORRELATION OF THE ELECTROCARDIOGRAPHIC EFFECTS WITH ELECTROLYTE ALTERATIONS. The electrocardiographic effects varied considerably depending upon the dose, rapidity of administration and the underlying clinical state. When 100 to 200 ml. of the molar sodium lactate was administered over a period of 10 to 15 minutes, the maximum electrocardiographic effects were usually observed toward the end of the infusion or within a few minutes thereafter[5]. When the infusion was given rapidly to patients with slow heart rates and in a state of shock, conspicuous effects were observed within 1 to 2 minutes. Aside from a rather rough correlation with the pH values, the electrocardiographic alterations could not usually be correlated with the electrolyte alterations. This lack of correlation may be due to the following factors: 1) the electrocardiographic alterations may be only partially due to electrolyte changes (alterations in acid-base balance, sodium, potassium and calcium) and may result from hemodynamic and nutritional changes due to the lactate radical; 2) the electrolyte changes occur relatively early and are initially localized in the heart where their initial effect is produced resulting in transient electrocardiographic alterations. Although these electrolyte changes may be rather profound, they are not necessarily mirrored by the serum electrolytes since considerable dilution occurs in the peripheral blood.

MOLAR SODIUM LACTATE AND EXTRASYSTOLES. The effect of this solution in either the production or abolition of premature beats or of paroxysmal tachycardia is of considerable interest. Of the 46 total cases studied to date in which this solution was administered, often in very large doses, ventricular extrasystoles were produced in only 4 cases. These appeared in the form of isolated premature beats or in the form of coupling. Their duration was extremely brief, lasting a few seconds or 2 minutes, at the most, and occurred at the height of the lactate effect.

The mechanism of the production of extrasystoles may be: a) sudden increase in cardiac work due to the lactate ion in a patient with a damaged heart; b) the production of alkalosis which tends to increase cardiac irritability; and c) in the presence of toxic digitalis effects an additional factor may be a further decrease of potassium in the heart muscle which may already be somewhat depleted of this electrolyte.

Of extreme interest is the fact that in the remainder of our entire group of patients who received similar and larger amounts and were followed over long periods of time (1 to 5 hours), 42 patients, many of whom also manifested severe grades of myocardial damage, failed to show extrasystoles. This is of considerable importance in comparison to the effect of epinephrine and other sympathomimetic drugs which manifest a marked tendency to produce extrasystoles and other ventricular arrhythmias. Ventricular extrasystoles which appeared in the form of continuous coupling, were abolished in one case for a period of about 2 hours following the administration of molar

sodium lactate. A similar finding was noted in dogs[6]. We are not certain as to the cause of their disappearance. The abolition of areas of decreased irritability or transient improvement in myocardial function or conduction, or both, within the heart muscle may be a factor.

EFFECTS IN NARROWING WIDENED QRS COMPLEXES. The narrowing of widened QRS complexes following the lactate administration is of considerable interest. This finding suggests that the ventricular pacemaker had shifted to a higher level and could be due to an increase in the conductivity of the heart muscle resulting from temporary improvement in the nutrition of the heart muscle or neuromuscular tissue, or both. Another factor is the alteration in the potassium-sodium ratio in the extracellular space. Failure to produce the effect might be the result of inadequate dosage or advanced and irreversible damage to the higher ventricular pacemakers.

MECHANISM OF CARDIAC EFFECTS. The possible mechanisms of the cardiac effects were discussed in some detail in a previous communication[5]. The exact mode has not yet been clearly established and investigations are in progress in an attempt to solve this problem. It is felt that the results observed are probably not due to vagolytic effects; nor do sympathomimetic effects adequately explain the phenomena observed. The possible influence of an increase in the serum sodium concentration in increasing the excitability of the cell has been mentioned as a possible cause of the increase in the heart rate. It is our impression, however, that the $NA^+$ ion, *per se*, is a minor factor in increasing the heart rate. This belief is based upon the fact that the increase in the serum sodium is relatively small with the doses of sodium lactate administered. It takes some time for this increase to occur and we have observed instances of increase in the serum sodium without demonstrable evidence of increased excitability or irritability. Our impression at this time is that the effects observed can best be explained by the production of alkalosis and the effect of the lactate.

**Summary.** The cardiovascular effects of the infusion of molar sodium lactate are discussed in the presence of various arrhythmias and compared with those observed in the normal heart. These manifestations were studied in a total of 32 patients. Included were normal subjects, patients with various types of myocardial abnormalities with normal sinus rhythm, partial A–V heart block, sinus bradycardia, carotid sinus hypersensitivity, extrasystoles and QRS widening, associated with various etiological factors (partial and complete A–V heart block and the idioventricular beats of cardiac arrest). In most of the subjects, the dose administered ranged from 100 to 200 ml. given in 10 to 15 minutes. The electrocardiographic changes were correlated with the blood pH, $CO_2$-combining power, lactic acid and the following electrolytes, sodium, potassium and calcium. Electrocardiographic alterations were observed chiefly in subjects with slow heart rates occurring with sinus bradycardia and partial and complete A–V heart block. Most of these patients showed evidence of an increase in the heart rate at the height of the sodium lactate effect; the maximum changes were usually observed at or within a few minutes after completion of the infusion. The occasional T wave and ST segment changes observed are believed to be the result of electrolyte alterations occurring in the heart following the infusion of sodium lactate.

This solution is fairly well tolerated and relatively few toxic manifestations were observed. In 3 subjects with ad-

vanced heart disease, transient extrasystoles were observed following the infusion. Extrasystoles present in another patient without evidence of organic heart disease were abolished following lactate administration.

There was no alteration in the degree of carotid sinus hypersensitivity in 4 subjects following the infusion of molar lactate.

The molar sodium lactate showed a definite tendency to narrow widened QRS complexes associated with partial and complete A–V heart block, bundle branch block and the idioventricular beats of cardiac arrest.

The mechanism of the clinical and electrocardiographic effects is discussed and their clinical significance is outlined.

REFERENCES

1. **Abramson, H. A.**, and **Eggleton, P.**: J. Biol. Chem., **75**, 753, 1927.
2. **Barker, S. B.**, and **Summerson, W. H.**: Ibid., **138**, 535, 1941.
3. **Bellet, S.**: Clinical Disorders of the Heart Beat. Philadelphia: Lea & Febiger, 1953.
4. **Bellet, S., Steiger, W. A., Nadler, C. S.**, and **Gazes, P. C.**: Am. J. Med. Sci., **219**, 542, 1950.
5. **Bellet, S., Wasserman, F.**, and **Brody, J. I.**: Circulation, **11**, 685, 1955.
6. Iidem: Work to be published.
7. **Clark, E. P.**, and **Collip, J. B.**: J. Biol. Chem., **63**, 461, 1925.
8. **Gilchrist, A. R.**: Brit. Med. J., **1**, 610, 1934.
9. Idem: Quart. J. Med., **2**, 463, 1937.
10. **Hartmann, A. E., Perley, A. M., Basman, J., Nelson, M. V.**, and **Asher, C.**: J. Pediat., **13**, 692, 1938.
11. **Haymond, T.**, and **Bellet, S.**: Am. J. Med., **16**, 516, 1954.
12. **Nathanson, M. H.**, and **Miller, H.**: Am. Heart J., **40**, 380, 1950.
13. **Neubauer, R. A.**: Am. J. Med. Sci., **228**, 656, 1954.
14. **Singer, R. B., Clark, J. K., Barker, E. S., Crosley, A. P., Jr.**, and **Elkinton, J. R.**: Medicine, **34**, 51, 1955.
15. **Van Slyke, D. D.**, and **Cullen, G. E.**: J. Biol. Chem., **30**, 289, 1917.
16. **Wilson, D. W.**, and **Bell, E. G.**: J. Biol. Chem., **79**, 221, 1928.

*(Interlingua on page 319)*

## SUMMARIO IN INTERLINGUA

*(See page 241 for original article)*

### Complicationes de Infection Meningococcal in un Serie de Sexanta-Tres Consecutive Casos Sporadic

Es presentate un reporto de 63 consecutive casos sporadic de infectiones meningococcal occurrente in recrutas del fortias aeree in le curso de un periodo de 4 annos. Iste patientes monstrava un alte procentage de complicationes. Le serie includeva 6 mortes, 4 debite al syndrome Waterhouse-Friderichsen. Cortisona intramuscular non pareva esser de grande adjuta in le tractamento. Norepinephrina esseva de valor plus immediate. Es notate le possibilitate que cortisona intravenose in administration plus prompte esserea de utilitate. Ben que le patientes esseva tractate promptemente con sulfadiazina e penicillina, 50 pro cento de illes habeva un o plure complicationes.

# THE USE OF IODIPAMIDE METHYLGLUCAMINE (CHOLOGRAFIN HIGH POTENCY) AS A CONTRAST MEDIUM FOR INTRAVENOUS CHOLANGIOGRAPHY

By J. Edward Berk, M.D., Sc.D.
DIRECTOR, DEPARTMENT OF MEDICINE, SINAI HOSPITAL OF DETROIT AND
ASSOCIATE PROFESSOR OF CLINICAL MEDICINE, WAYNE UNIVERSITY COLLEGE OF MEDICINE

Harry Z. Mellins, M.D.
DIRECTOR, DEPARTMENT OF RADIOLOGY, SINAI HOSPITAL OF DETROIT AND
CLINICAL ASSISTANT PROFESSOR OF RADIOLOGY, WAYNE UNIVERSITY COLLEGE OF MEDICINE

AND

Marvin Brodie, M.D.
RESIDENT IN MEDICINE, SINAI HOSPITAL OF DETROIT

(From the Departments of Medicine and Radiology, Sinai Hospital of Detroit and the Wayne University College of Medicine, Detroit, Michigan)

The development and introduction of iodipamide sodium (Biligrafin [Schering, A. G.]; Cholografin [E. R. Squibb & Sons])[2,6], an iodinated radiopaque medium that may be safely given intravenously and is promptly and rapidly excreted by the liver, answered the need for a reliable nonsurgical means of roentgenologically visualizing the biliary ducts. It probably was to be anticipated that other media possessing certain advantages over iodipamide sodium would be evolved in time. Reports have now appeared on the use of a 40% solution of a lithium salt of iodipamide (Biligrafin forte; Biligrafin 40% [Schering, A. G.])[3,9,11]. Iodipamide methylglucamine (Cholografin High Potency [E. R. Squibb & Sons])* is a still more recently developed modification of the original cholangiographic medium[3]. We wish to report our experiences to date with this newer preparation.

**Material and Method.** Cholografin is the di-sodium salt of N, N, adipyl-bis (3-amino-2:4:6 triiodobenzoic acid). Cholografin High Potency is the methylglucamine salt of the same chemical agent and is more soluble than the sodium salt. It has a molecular weight of 1,584 and an iodine content of approximately 48%[7]. As prepared for clinical use, Cholografin High Potency consists of a 52% weight/volume solution of the methylglucamine salt with a pH range of from 6.0 to 6.5. It is supplied in ampules containing 20 ml. of the 52% solution of the methylglucamine salt. This is essentially equivalent to a 40% solution of Cholografin.

The pharmacological properties of Cholografin High Potency are the same as those of Cholografin. It is similarly promptly and rapidly excreted by the liver following intravenous administration. As with Cholografin, it is also eliminated principally in the feces. Only some 10% or less of the material is purportedly excreted through the kidneys, except in the presence of hepatic impairment when a much larger proportion is excreted in the urine.

Acute and chronic toxicity studies conducted in a variety of experimental animals have indicated that Cholografin High Potency is of a low order of toxicity[4,7,12]. The toxicity of N-methylglucamine and of compounds containing methylglucamine have also been demonstrated to be low in laboratory animals[1,5,8,10].

In the 4-month period from March to July, 1955, 82 studies were conducted on 74

*Kindly supplied by Dr. Mark H. Lund, Associate Medical Director, The Squibb Institute for Medical Research, New Brunswick, N. J.

subjects. These were divided into 3 groups. The first group (Group A) was made up of 10 subjects. Three of these subjects had a normal biliary tree, one had symptomatic cholelithiasis, 3 had been cholecystectomized (2 with current symptoms suspected of being biliary in origin), one had viral hepatitis, one had cholangiolitic hepatitis, and one had portal cirrhosis and extrahepatic biliary obstruction. Each subject received ordinary Cholografin and Cholografin High Potency on different days in order to compare the quality and extent of ductal visualization. Serum bilirubin levels were determined and hepatic function was evaluated in each subject just prior to the examinations. In most cases there was an interval of one day between the examinations but in some cases the examinations were conducted on consecutive days.

The second group (Group B) consisted of 3 patients in whom a single intravenous cholangiographic study was carried out with Cholografin High Potency. None of these 3 patients had had their gallbladders removed and each was purposely selected because of the presence of either obstructive jaundice (1 patient) or hepatic derangement without jaundice (2 patients).

The third group (Group C) consisted of 61 unselected subjects, both with and without gallbladders. They represented a series of consecutively examined persons who had been referred to the Radiology Department expressly for intravenous cholangiography. In 34 persons of this group the gallbladder was intact; in 27 the gallbladder had been previously removed.

A preliminary roentgenogram of the right upper quadrant of the abdomen was made in each subject. While the film was being developed, a test dose of 1 ml. of Cholografin High Potency was given intravenously and the subject was then observed for approximately 10 minutes. If no untoward reaction developed, the contrast medium was slowly injected intravenously. The 10 subjects on whom comparative studies were made each received 40 ml. of ordinary Cholografin; on the second study 8 were given 20 ml. of Cholografin High Potency and 2 received 40 ml. of Cholografin High Potency. One of the 64 subjects who were examined only with Cholografin High Potency was given 40 ml. of this preparation; the remainder received 20 ml. of the medium. Approximately 8 minutes were taken to inject the material when the dose was 40 ml.; the material was given over a period of from 4 to 5 minutes when the dose was 20 ml.

Immediately following completion of the intravenous injection, a roentgenogram was made. Serial roentgenograms were then made in Group A every 10 minutes for 1 hour, at 1½ hours, at 2 hours, and at 2½ hours. In Groups B and C serial roentgenograms were exposed at less frequent intervals and usually over a period no longer than 1 hour. The period of observation was shortened in Groups B and C because primary interest centered on visualization of the extrahepatic ducts since each subject in these groups either had been cholecystectomized or had previously been studied by oral cholecystography.

In all cases a Potter-Bucky diaphragm was used. The Roentgen factors were 300 milliamperes and 0.5 second exposure; the kilovoltage varied with the thickness of the individual and was computed according to the formula of twice the body thickness in cm. plus 21. Each subject was placed in a 15 degree right posterior oblique supine position. The position of the subject was subsequently changed as required to displace the shadow of the common bile duct from that of the spine. Such changes were made depending on the situation disclosed by the roentgenograms on which the duct was first seen. Three exposures of increasing obliquity were routinely made when the duct was optimally opacified. This maneuver was found to be a useful way to project the duct away from interfering gas shadows. It also permitted stereoscopic viewing. A small cone was used to reduce stray radiation. The focal film distance in each case was 36 inches.

**Results.** GROUP A. The biliary ducts were slightly better visualized after the administration of Cholografin High Potency than after ordinary Cholografin in 5 of the 10 subjects on whom comparative examinations were made. In a sixth subject, a patient with portal cirrhosis and extrahepatic biliary obstruction whose total serum bilirubin was 7.5 mg. per 100 ml. at the time of study, the biliary tract failed to visualize after ordinary Cholografin but both the gallbladder and common duct were seen after 20 ml. of Cholografin High Potency. The cholangiograms appeared to be essentially the same in 3 subjects. No comparison could be made in the final subject because the films

taken when ordinary Cholografin was given were technically poor.

GROUP B. The gallbladder and bile ducts were adequately visualized after the intravenous injection of 20 ml. of Cholografin High Potency in both patients whose hepatic function was known to be impaired. Neither the gallbladder nor the ducts could be seen in the patient with obstructive jaundice.

GROUP C. The bile ducts were satisfactorily opacified in 22 of the 34 subjects whose gallbladders were intact. The ducts of the remaining 12 subjects with intact gallbladders either failed to visualize or were very faintly visualized. Eight of these 12 patients were known to have hepatic disease of various types (with or without jaundice), 2 had obstructive jaundice, and one was recovering from acute pancreatitis; there was no apparent reason for the poor results in only 1 of the 12.

Visualization of the extrahepatic ducts was satisfactory in 21 of the 27 subjects whose gallbladders had been removed. Of the 6 cholecystectomized subjects whose ducts were not visualized or were poorly visualized, 4 had obstructive jaundice (one with associated biliary cirrhosis), one had a draining T-tube in the common duct (contrast medium was noted in the collecting arm of the tube), and one was a diabetic with chronic relapsing pancreatitis.

As measured by the degree and extent of opacification of the extrahepatic ductal system, the intravenous cholangiograms obtained in this group were at least equal to, and in some cases surpassed those previously obtained by us after the administration of ordinary Cholografin to similarly unselected and consecutively studied subjects.

REACTIONS. Systemic reactions were observed in all 3 of the subjects who were given 40 ml. of Cholografin High Potency. Because of these occurrences, we were reluctant to use doses larger than 20 ml. in the remainder of our study. The reaction in the first subject given 40 ml. of Cholografin High Potency consisted of a generalized urticarial eruption that persisted despite treatment and finally resulted in patchy areas of chronic dermatitis. The second patient developed a transient feeling of warmth immediately after injection. Two and one-half hours later there was weakness and chilliness. Examination at this time revealed atrial extrasystoles. The systemic symptoms and the cardiac irregularity spontaneously subsided after 1½ hours and the patient was well thereafter. The third patient, who was suffering from a drug-induced cholangiolitic form of hepatitis associated with jaundice, developed chilliness soon after injection. This persisted for approximately 20 minutes and then spontaneously subsided.

Only one of the 71 subjects to whom a total of 79 injections of 20 ml. of Cholografin High Potency were given, showed any untoward systemic reaction. The reaction in this patient consisted of chills and nausea appearing shortly after injection and persisting for 7 hours. At this time, the patient developed syncope, nuchal rigidity, and clenched jaws which lasted for 5 minutes. Following this she felt better but was still not entirely well. By the following morning she had fully recovered and remained well thereafter.

None of the subjects showed any evidence of local irritation or of phlebitis at the site of injection of the contrast medium.

**Discussion.** The degree of opacification of the biliary ducts following 20 ml. of a more concentrated preparation of Cholografin (Cholografin High Potency) appears to be at least equal to that after a total dosage of twice as much ordinary Cholografin. The ability to obtain equivalent opacifica-

tion of the ducts with only half the volume of contrast medium ordinarily used is an advantage.

Since 20 ml. of Cholografin High Potency and 40 ml. of ordinary Cholografin provide essentially identical amounts of chemically similar iodine-containing contrast medium, liver disease and extrahepatic obstructive jaundice would be expected to interfere as much with hepatic excretion of the latter as they do with the former. The frequency with which such disorders were found in those of our subjects whose ducts were unsatisfactorily visualized after 20 ml. of Cholografin High Potency lends support to this expectation. On the other hand, it is of considerable interest to note that in one of our subjects the biliary ducts were not visualized after the 20% preparation but did become opacified after the 40% preparation. This was all the more remarkable because the patient had portal cirrhosis and extrahepatic biliary obstruction with a total serum bilirubin measuring 7.5 mg. per 100 ml. at the time of study. The comparative studies were performed only a day apart, so that there was little likelihood of significant change in the level of bilirubinemia or in the degree of hepatic derangement. We were all the more impressed by this occurrence because successful visualization of the extrahepatic ducts in a subject with hepatic disease of this severity and with hyperbilirubinemia of this magnitude was unique in our experience. Successful visualization of the biliary ducts in the 2 subjects who were purposely studied because of impaired hepatic function is also of considerable interest. These observations suggest the possibility that in the occasional patient with hepatic derangement or extrahepatic obstructive jaundice, Cholografin High Potency may succeed in visualizing the gallbladder or biliary ducts when ordinary Cholografin may fail to do so. The likelihood of this occurring may be even greater if the patient is able to tolerate doses of Cholografin High Potency greater than 20 ml.

It may safely be stated that the 40% Cholografin preparation is tolerated as well by human subjects as is 20% Cholografin when the former is given in amounts of 20 ml. The systemic reactions that were observed in the 3 subjects who received doses of 40 ml. of Cholografin High Potency gave us concern and made us reluctant to utilize doses larger than 20 ml. until we had acquired a larger experience with the use of the preparation. It may well have been that these occurrences were simply coincidental and that doses larger than 20 ml. may safely be given to human subjects, provided there is careful questioning about an allergic state or iodine sensitivity beforehand and provided that the material is administered slowly and only to those who show no reaction to a preliminary test dose.

In a number of instances we had the impression that the ducts were seen more promptly than had been our general experience with ordinary Cholografin, but this was variable and inconstant. It was our impression, too, that Roentgen visualization of portions of the drainage system of the kidneys occurred a little earlier and perhaps to a greater degree than with ordinary Cholografin.

**Summary and Conclusions.** 1. Cholografin High Potency may be safely given to human subjects in doses of 20 ml. The reaction rate following the administration of 20 ml. of this material is small and is probably no different from that after ordinary Cholografin.

2. Cholografin High Potency in doses of 20 ml. opacifies the biliary ducts to a degree at least equal to that after

ordinary Cholografin given in doses of 40 ml. The ability to obtain satisfactory and comparable cholangiograms with significantly smaller volumes of contrast medium is an advantage.

3. Cholografin High Potency in doses of only 20 ml. may permit Roentgen visualization of the extrahepatic biliary tree in some patients with hepatic impairment or obstructive jaundice. The likelihood of successful visualization of the biliary tree in such patients may be enhanced if doses larger than 20 ml. can be tolerated.

## REFERENCES


1. Commercial Solvents Corporation, Market Development Department. Technical Data Sheet 1052 MD–5, p. 4 (V. F. Glucamine, N-methyl-), Cited by **Lund**[7].
2. **Frommhold, W.**: Fortschr. Geb. Röntgenstrahlen, **79**, 283, 1953.
3. **Gaebel, E.**, and **Teschendorf, W.**: Ibid., **81**, 296, 1954.
4. **Hunt, W. H.**: Report of Pharmacological Tests. The Squibb Institute for Medical Research, December 27, 1954. Cited by **Lund**[7].
5. Idem: Toxicity of N-methylglucamine. The Squibb Institute for Medical Research, July 16, 1954. Cited by **Lund**[7].
6. **Langecker, H., Harwart, A.**, and **Junkmann, K.**: Arch. exper. Path. u. Pharmakol., **220**, 195, 1953.
7. **Lund, M. H.**: Technical Information supplied by M. H. Lund, The Squibb Institute for Medical Research, New Brunswick, N. J.
8. **Maloney, A. H.**: J. Lab. & Clin. Med., **28**, 38, 1942.
9. **Oeser, H.**, and **Frommhold, W.**: Acta radiol., **43**, 355, 1955.
10. **Sewell, P.**, and **Hawkins, F.**: Brit. J. Pharmacol. & Chemotherap., **5**, 238, 1950.
11. **Theander, G.**: Acta radiol., **43**, 369, 1955.
12. **Thomas, B. G. H.**: Pharmacological Studies on High Potency Cholografin. The Squibb Institute for Medical Research, April 19, 1955. Cited by **Lund**[7].


## SUMMARIO E CONCLUSIONES IN INTERLINGUA

### Le Uso de Iodipamido-Methylglucamino (Cholografin a Alte Potentia) Como Substantia de Contrasto pro Cholangiographia Intravenose


1. Cholografin a Alte Potentia pote administrar se sin risco a humanos in doses de 20 ml. Le reactiones post le administration de 20 ml de iste substantia non es extense e probabilemente non differe ab le grado del reactiones post Cholografin ordinari.

2. Cholografin a Alte Potentia in doses de 20 ml opacifica le vias biliari a un grado al minus équal a illo obtenite per Cholografin ordinari in doses de 40 ml. Le possibilitate de obtener satisfacente cholangiogrammas de non reducite qualitate per medio de significativemente reducite volumines del substantia de contrasto es un avantage.

3. Cholografin a Alte Potentia in doses de non plus que 20 ml pote permitter le visualisation roentgenologic del extrahepatic arbore biliari in certe patientes con alterationes hepatic o ictero obstructive. Le probabilitate de successo in le visualisation del arbore biliari in tal patientes es augmentate si doses de plus que 20 ml es tolerate.

# THE EFFECT OF PENTOLINIUM ON RENAL HEMODYNAMICS AND WATER AND ELECTROLYTE EXCRETION: A COMPARISON WITH HEXAMETHONIUM*†

By John H. Moyer, M.D.
ASSOCIATE PROFESSOR OF PHARMACOLOGY AND MEDICINE

AND

Robert L. Hershberger, M.D.
SENIOR RESIDENT IN CARDIOLOGY

WITH THE TECHNICAL ASSISTANCE OF
C. Polk Smith and Elizabeth Houston

(From the Cardiac Clinic of the Jefferson Davis Hospital and the Departments of Pharmacology and Medicine, Baylor University College of Medicine, Houston, Texas)

In the treatment of patients with hypertensive vascular disease, many procedures designed to interrupt sympathetic nervous system pathways have been used. At the present time, drugs which produce adrenergic and ganglionic blockade are receiving more and more attention. One of the newer agents to be used for this purpose is pentolinium (Ansolysen), a drug which blocks the transmission of impulses through the ganglia of the autonomic nervous system apparently by raising the response threshold of the ganglia cells to acetylcholine which is released by the preganglionic nerve endings. Although hexamethonium, which also acts in this manner, has been found to be effective in reducing the blood pressure in hypertensive patients, incomplete intestinal absorption has led to the use of other agents such as pentolinium, which will be less variable in their blood pressure effect. Pentolinium has been found to have essentially the same response in laboratory animals as does hexamethonium but the drug is considerably more potent[4] and the length of action is 2 to 3 times that of hexamethonium[1]. Therefore, an evaluation of the effects of pentolinium on the kidneys in both normal human subjects and patients with hypertension was undertaken since this drug is being used so widely for the treatment of hypertension[1].

**Methods and Materials.** NORMAL CONTROL SUBJECTS: GROUP 1. Following adequate control observations, pentolinium (Ansolysen)** was administered by continuous intravenous infusion to 9 normal control subjects. The blood pressure was within normal limits in all of these patients. The pentolinium was placed in 5% glucose in distilled water and was administered at a rate of 70 micrograms (mcg.) to as much as 3.1 mg. per minute, depending upon the blood pressure response. The rate of the infusion was regulated by the minimum amount of drug which would produce a maximum reduction in blood pressure. The infusion was continued for a period of 3 hours. During this period of time, the

*Presented before the Southern Society for Clinical Research by Dr. R. L. Hershberger, January 29, 1955.

†Supported in part by a grant from the Houston Heart Association and the Medical Research and Development Board, Office of the Surgeon General, Dept. of the Army under contract number DA–49–007–MD–314.

**Furnished by Wyeth Laboratories.

total amount of drug given varied from 10 to 88 mg. depending upon the rate of infusion which was required. Glomerular filtration rate was determined using the inulin clearance technique and renal blood flow was determined by para-aminohippurate clearance. Sodium and potassium excretion rates were determined using a Beckman flame photometer for analyses. Three consecutive 10-minute periods were used for control observations, each patient thus serving as his own control. After the drug administration was begun, consecutive 10-minute collection periods were obtained for the next 3 hours. Mean blood pressure was determined by intra-arterial manometry. Details of the techniques and analytical procedures have previously been reported[2,3].

HYPERTENSIVE PATIENTS WHO WERE GIVEN PENTOLINIUM: GROUP 2. Following the studies of normal control subjects, pentolinium was then administered to 16 patients with hypertension. These 16 patients were divided into 2 subgroups (2A and 2B). Subgroup 2A consisted of 8 patients who received pentolinium by continuous infusion similar to the normotensive control subjects and subgroup 2B consisted of 8 patients who received pentolinium as a single intravenous injection. The total doses by each method are tabulated in Table 2A. The rate of infusion for the patients in group 2A was adjusted so as to produce the maximum reduction in blood pressure with a minimum amount of drug. The rate of infusion varied from 80 mcg. per minute to as much as 3 mg. per minute and was continued for 3 hours or more. Patients unresponsive to small doses of pentolinium received relatively large amounts of the drug over the 3-hour period. For the patients in Group 2B who were given the drug by single injection, the drug was given in 12.5 mg. increments over a 20-minute period. If maximum blood pressure reduction was obtained, only 25 mg. were given. If it appeared that greater blood pressure reduction was possible, additional 12.5 mg. increments were given to a maximum total dose of 50 mg. In one patient, the blood pressure reduction was so marked with the first 12.5 mg. dose that additional drug was not given. Consecutive 10-minute collection periods were obtained during a 30-minute control period and for the next 3 hours after drug administration during which time the effects of blood pressure reduction on renal hemodynamics and water and electrolyte excretion were studied. The observations obtained on the patients in Subgroup 2B were then compared with those obtained on the patients to whom the drug was administered by continuous intravenous infusion (Subgroup 2A).

HYPERTENSIVE PATIENTS WHO WERE GIVEN HEXAMETHONIUM: GROUP 3. In order to compare the renal effects of pentolinium with hexamethonium, the latter drug was administered by continuous intravenous infusion to 8 patients with hypertension. Following adequate control observations (three 10-minute periods), hexamethonium was infused at a rate ranging from 200 mcg. per minute to 2 mg. per minute. As with the pentolinium, the rate of infusion was adjusted so as to obtain a maximum reduction in blood pressure with as little drug as necessary. Successive 10-minute collection periods were obtained for 3 hours during the infusion of hexamethonium. The total amounts of drug infused are indicated in Table 3A. These observations were then compared with those made on the patients in Group 2A.

**Results.** GROUP 1. The effects on renal hemodynamics in the normotensive subjects are summarized in Table 1A and the effects on water and electrolyte excretion are summarized in Table 1B.

Within 10 minutes following the beginning of the infusion, the blood pressure usually showed some reduction from the control values. However, the maximum reduction was not observed for the group until one hour after the infusion was begun. At this time, the average for the group had decreased to 70% of the control and was not reduced any further irrespective of the rate of infusion. It remained within this range throughout the study which response was statistically significant ($p<0.001$).

As the blood pressure decreased, there was a significant reduction in glomerular filtration rate which remained depressed throughout the study period and reached the highest statistical significance ($p<0.001$) at the 2-hour period after beginning the infusion although the average absolute value was lower at the 1-hour period. There was very little, if any, tendency towards compensation after 3 hours.

Associated with the reduction in glomerular filtration rate there was a similar reduction in renal blood flow which was greatest during the first hour and then gradually returned towards the control level despite a maintained reduction in blood pressure for 2 to 3 hours. Only the initial reduction in renal blood flow was statistically significant ($p<0.05$). Due to the variability of response, there was no significant effect on renal vascular resistance for the group.

Associated with the reduction in glomerular filtration rate there was a significant reduction in urine volume and sodium excretion, ($p<0.01$). This persisted throughout the study and in no instance did it tend to return to the control level. There was no effect on the plasma concentration of sodium. Although there was a definite reduction in potassium excretion, this response was not great enough ($p<0.10$) to be statistically significant. There was a reduction in the plasma concentration of potassium probably due to the infusions being administered.

GROUP 2. The observations made following continuous infusion of pentolinium as compared to a single injection given to patients with hypertension are presented in Tables 2A to 2C. The reduction in blood pressure was more rapid following the single intravenous injection of pentolinium than following the continuous intravenous infusion. This is to be anticipated since the initial amount of drug received was much greater following the single injection than following the continuous infusion, thus establishing a threshhold blood level (blocking dose) more rapidly. However, over the 3-hour period of study, the amount of drug received by the patients being given the continuous infusion was often considerably greater than it was in the patients receiving the drug as a single

TABLE 1A.—EFFECT OF CONTINUOUS INFUSION OF PENTOLINIUM ON RENAL HEMODYNAMICS IN NORMAL SUBJECTS

| Patient | Mean Blood Pressure mm. Hg | | | | | Renal Blood Flow† ml./min. | | | | | Renal Vascular* Resistance | | | | | Total Dose Pentolinium mg. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | |
| 1. L.S. | 99 | 90 | 62 | 51 | 52 | 983 | 294 | 229 | 280 | 243 | 35 | 31 | 27 | 18 | 21 | 40 |
| 2. L.O. | 106 | 105 | 91 | 82 | 95 | 654 | 718 | 708 | 597 | 856 | 16 | 15 | 13 | 14 | 11 | 88 |
| 3. A.R. | 94 | 67 | 52 | 62 | 65 | 967 | 670 | 241 | 953 | 1003 | 10 | 10 | 22 | 07 | 06 | 10 |
| 4. J.S. | 110 | 110 | | 100 | 90 | 642 | 560 | | 804 | 481 | 17 | 20 | | 12 | 19 | 70 |
| 5. L.McD. | 101 | 75 | 63 | 71 | 72 | 722 | 488 | 583 | 697 | 697 | 14 | 15 | 11 | 10 | 10 | 25 |
| 6. M.P. | 94 | 82 | 71 | 73 | 82 | 1044 | 860 | 464 | 533 | 739 | 09 | 10 | 15 | 14 | 11 | 75 |
| 7. L.D. | 85 | 81 | 72 | 70 | 73 | 788 | 610 | 628 | 578 | 643 | 11 | 13 | 11 | 12 | 11 | 55 |
| 8. A.W. | 91 | 71 | 67 | 67 | 70 | 963 | 330 | 1073 | 808 | 860 | 09 | 22 | 06 | 08 | 08 | 63 |
| 9. J.C. | 95 | 86 | 69 | 69 | 76 | 707 | 698 | 636 | 552 | 511 | 13 | 12 | 11 | 13 | 15 | 75 |
| Mean per cent of control | 97 | 85 | 68 | 72 | 75 | 752 | 581 | 570 | 645 | 670 | 15 | 16 | 15 | 12 | 12 | |
| | | 88 | 70 | 74 | 77 | | 77 | 76 | 86 | 89 | | 107 | 100 | 80 | 80 | |
| P Value‡ | | 01 | 001 | 001 | 001 | | 05 | 30 | 20 | 20 | | NS | NS | 20 | 30 | |

| Patient | Glomerular Filtration Rate ml./min. | | | | | Renal Plasma Flow** ml./min. | | | | | Filtration Fraction†† | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ |
| 1. L.S. | 42 | 44 | 30 | 31 | 18 | 201 | 209 | 165 | 207 | 182 | .21 | .21 | .18 | .15 | .10 |
| 2. L.O. | 59 | 61 | 57 | 49 | 58 | 425 | 467 | 460 | 382 | 548 | .14 | .13 | .12 | .13 | .11 |
| 3. A.R. | 76 | 45 | 11 | 58 | 79 | 609 | 422 | 154 | 610 | 652 | .12 | .11 | .07 | .10 | .12 |
| 4. J.S. | 93 | 59 | ... | 83 | 57 | 424 | 375 | ... | 539 | 322 | .22 | .16 | ... | .15 | .18 |
| 5. L.McD. | 86 | 58 | 64 | 67 | 94 | 484 | 327 | 379 | 460 | 467 | .18 | .18 | .17 | .15 | .20 |
| 6. M.P. | 99 | 80 | 57 | 73 | 105 | 595 | 490 | 283 | 325 | 436 | .17 | .16 | .20 | .23 | .24 |
| 7. L.D. | 173 | 185 | 150 | 156 | 134 | 536 | 415 | 427 | 393 | 437 | .32 | .45 | .35 | .40 | .31 |
| 8. A.W. | 120 | 59 | 103 | 105 | 103 | 616 | 234 | 794 | 598 | 559 | .19 | .25 | .13 | .18 | .18 |
| 9. J.C. | 117 | 118 | 89 | 101 | 89 | 382 | 384 | 369 | 320 | 286 | .31 | .31 | .24 | .32 | .31 |
| Mean per cent of control | 96 | 79 | 70 | 80 | 82 | 475 | 369 | 379 | 426 | 432 | .21 | .22 | .18 | .20 | .19 |
| P Value‡ < | | .10 | .01 | .001 | .10 | | .05 | .20 | NS | .10 | | NS | .20 | NS | NS |

FOOTNOTES:

† = Renal blood flow = $\frac{\text{Renal plasma flow}}{1-\text{hematocrit}}$

* = Renal vascular resistance = $\frac{\text{Mean blood pressure}}{\text{Renal blood flow}}$

** = Para-aminohippurate clearance

†† = Filtration fraction = $\frac{\text{Glomerular filtration rate}}{\text{Renal plasma flow}}$

‡ = $t = x\sqrt{\frac{n\,(n-1)}{Sx^2}}$ Statistical analysis by R. A. Seibert, Ph.D.

Group 1—Normotensive, control subjects
C = Control; average of three 10-minute periods
$D_1$ = Observations during first 30 minutes after starting drug infusion; average three 10-minute periods
$D_2$ = Observations made one hour after beginning infusion; average of two 10-minute periods
$D_3$ = Observations made 2 hours after beginning infusion; average of two 10-minute periods
$D_4$ = Observations made 3 hours after beginning infusion, average of two 10-minute periods
NS = P Value > 0.30

TABLE 1B.—EFFECT OF CONTINUOUS INFUSION OF PENTOLINIUM ON WATER AND ELECTROLYTE EXCRETION IN NORMAL SUBJECTS

| *Patient* | *Age* | *Race* | *Sex* | *Urine Volume ml./min.* | | | | | *Sodium Excretion μEq./min.* | | | | | *Potassium Excretion μEq./min.* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ |
| 1. L.S. | 60 | C | F | 5.3 | 6.0 | 1.3 | 0.5 | 0.5 | 144 | 113 | 46 | 97 | 10 | 23 | 27 | 33 | 48 | 45 |
| 2. L.O. | 36 | C | F | 11.6 | 11.7 | 9.5 | 1.5 | 1.9 | 145 | 150 | 134 | 90 | 177 | 32 | 31 | 25 | 22 | 37 |
| 3. A.R. | 62 | C | F | 11.5 | 5.2 | 0.2 | 0.3 | 0.6 | 183 | 95 | 9 | 11 | 24 | 117 | 62 | 6 | 15 | 23 |
| 4. J.S. | 18 | C | F | 9.8 | 2.7 | ... | 2.3 | 0.5 | 146 | 152 | ... | 174 | 72 | 28 | 14 | ... | 19 | 13 |
| 5. L.McD. | 48 | C | F | 2.2 | 1.5 | 0.6 | 0.6 | 0.8 | 221 | 103 | 65 | 101 | 82 | 29 | 19 | 28 | 36 | 31 |
| 6. M.P. | 27 | C | F | 3.0 | 5.5 | 0.8 | 0.3 | 0.2 | 59 | 28 | 14 | 16 | 14 | 69 | 58 | 36 | 52 | 60 |
| 7. L.D. | 19 | C | M | 4.7 | 8.9 | 0.9 | 0.2 | 0.4 | 335 | 179 | 87 | 19 | 112 | 151 | 160 | 111 | 131 | 76 |
| 8. A.W. | 16 | C | F | 3.4 | 1.8 | 0.6 | 0.6 | 0.5 | 314 | 91 | 33 | 23 | 34 | 96 | 44 | 91 | 87 | 77 |
| 9. J.C. | 19 | C | M | 5.5 | 7.5 | 3.0 | 1.8 | 0.8 | 364 | 293 | 116 | 88 | 75 | 132 | 158 | 82 | 61 | 31 |
| Mean | 34 | | | 6.3 | 5.6 | 2.1 | 0.9 | 0.7 | 212 | 134 | 63 | 69 | 67 | 75 | 64 | 52 | 52 | 44 |
| Per cent of control | | | | | 89 | 33 | 14 | 11 | | 63 | 30 | 33 | 32 | | 85 | 69 | 69 | 59 |
| P Value < | | | | | NS | .05 | .01 | .01 | | .05 | .01 | .05 | .01 | | .20 | .10 | .20 | .10 |

| | *Hematocrit* | | | | | *Plasma Sodium mEq./L.* | | | | | *Plasma Potassium mEq./L.* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ |
| Mean value (9 patients) | 36 | 35 | 34 | 34 | 35 | 139 | 138 | 138 | 138 | 137 | 5.0 | 4.8 | 4.9 | 4.6 | 4.2 |
| Per cent of control | | 97 | 94 | 94 | 97 | | 99 | 99 | 99 | 99 | | 96 | 98 | 92 | 84 |
| P Value < | | .30 | .20 | .05 | .10 | | .20 | NS | NS | .30 | | .30 | .30 | .01 | .01 |

Key: C–$D_4$ see Table 1A for key to abbreviations. C = Negro F = Female M = Male

injection yet the blood pressure response was no greater indicating that a "floor" in the blood pressure had been reached beyond which it was not possible to lower the blood pressure despite the larger amounts of drug being given. By the end of 2 hours, the degree of blood pressure reduction was about the same irrespective of the manner in which the drug had been given. By the end of the third hour, the blood pressure remained identical for both groups and the changes were highly significant ($p<0.001$).

The manner of drug administration was also reflected in the renal blood flow response. Following the single injection there was a much greater initial percentile reduction in renal blood flow but after 2 hours, the renal blood flow had returned to control levels. However, after the continuous infusion, the depression in renal blood flow reached its maximum during the first 30 minutes and it remained somewhat depressed throughout the study. In fact, renal blood flow did not return to the control levels in the patients receiving continuous infusion of pentolinium until norepinephrine was administered and the blood pressure was increased to mild hypertensive levels which approximated the control levels in some of the cases. At no time was there a significant reduction in renal vascular resistance for those patients receiving the drug as a continuous intravenous infusion. However, following the single injection, the renal vascular resistance decreased significantly 2 to 3 hours after drug administration.

Blood pressure reduction was associated with a significant reduction in glomerular filtration rate (Table 2B). Immediately after the single injection of pentolinium, there was a significant reduction, ($p<0.01$) in glomerular filtration rate to 60% of the control value and this remained depressed throughout the study. During the continuous infusion of pentolinium, the glomerular filtration rate was reduced but this was not statistically significant until one to two hours after beginning the infusion. It then remained depressed throughout the study. When the blood pressure was increased with norepinephrine, glomerular filtration rate returned to or toward the control value.

The reduction in glomerular filtration rate was associated with a striking reduction in water and sodium excretion (Table 2C). This occurred after both the continuous intravenous infusion as well as following the single injection of pentolinium. The rapidity of onset of blood pressure reduction by the two methods of drug administration is again reflected in the reduction in urine volume and sodium excretion. These were not depressed significantly ($p<0.05$) until one to two hours after beginning the intravenous infusion to the patients in Group 2A whereas after the single injection, these functions were depressed immediately ($p<0.05$) and remained depressed throughout the study. There was no significant effect on potassium excretion. These patients also showed a reduction in plasma sodium ($p<0.05$) and potassium concentrations ($p<0.01$). A reduction in concentration of these electrolytes in the plasma is frequently seen following infusions, particularly infusions of para-aminohippurate or glucose.

GROUP 3. In order to compare the renal hemodynamic response of pentolinium to hexamethonium, the latter was administered by continuous intravenous infusion to 8 patients with hypertension in a manner similar to the 8 hypertensive patients who received pentolinium by continuous intravenous infusion. These results are tabulated in Tables 3A and 3B. The average blood pressure for the group was reduced from 132 mm. to 91 mm. Hg at the point

TABLE 2A.—RENAL HEMODYNAMIC RESPONSE TO PENTOLINIUM: COMPARING CONTINUOUS INFUSION WITH SINGLE INJECTION IN PATIENTS WITH HYPERTENSION

| Patient | *Mean Blood Pressure*** mm. Hg | | | | | | *Renal Blood Flow*† ml./min. | | | | | | *RVR*‡ ml./min. | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Group A* | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *NE*° | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *NE*° | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *NE*° | *Total* |
| CONTINUOUS INFUSION OF PENTOLINIUM | | | | | | | | | | | | | | | | | | | |
| 1. L.H. | 136 | 118 | 68 | 66 | 66 | 120 | 761 | 484 | 71 | 80 | 222 | 1530 | .18 | .24 | .96 | .83 | .30 | .08 | 15.0 |
| 2. A.McD. | 164 | 164 | 128 | 93 | 95 | 128 | 205 | 213 | 160 | 129 | 147 | 262 | .80 | .77 | .80 | .72 | .65 | .49 | 37.2 |
| 3. L.B. | 152 | 144 | 115 | 100 | 96 | 114 | 285 | 285 | 229 | 217 | 288 | 330 | .53 | .51 | .50 | .46 | .33 | .35 | 145.0 |
| 4. M.T. | 138 | 104 | 73 | 65 | 70 | 113 | 789 | 541 | 889 | 750 | 817 | 861 | .17 | .19 | .08 | .09 | .09 | .13 | 10.0 |
| 5. M.Y. | 158 | 100 | 97 | 91 | 99 | 125 | 667 | 276 | 747 | 650 | 680 | 722 | .24 | .36 | .13 | .14 | .15 | .17 | 82.8 |
| 6. S.L. | 144 | 143 | 101 | 115 | 121 | 147 | 809 | 675 | 497 | 522 | 528 | 810 | .18 | .21 | .20 | .22 | .23 | .18 | 196.0 |
| 7. L.M. | 119 | 118 | 106 | 94 | 94 | 124 | 614 | 681 | 734 | 861 | 541 | 484 | .19 | .17 | .14 | .11 | .17 | .26 | 152.0 |
| 8. G.R. | 127 | 123 | 96 | 79 | 74 | ... | 448 | 403 | 281 | 407 | 393 | ... | .28 | .31 | .34 | .19 | .19 | ... | 127.0 |
| Mean | 142 | 127 | 98 | 88 | 89 | 124 | 572 | 445 | 451 | 452 | 452 | 714 | .32 | .35 | .39 | .35 | .26 | .24 | |
| Per cent of control | | 89 | 69 | 62 | 63 | 87 | | 78 | 79 | 79 | 79 | 125 | | 109 | 122 | 109 | 81 | 75 | |
| P Value* < | | .10 | .001 | .001 | .001 | .05 | | .05 | .30 | .30 | .20 | .20 | | NS°° | NS°° | NS°° | .10 | .20 | |
| P Value* < [d] | | | | | | .001[d] | | | | | | .30[d] | | | | | | .40[d] | |
| *Group B* | | | | | | | | | | | | | | | | | | | *Total* |
| SINGLE INJECTION OF PENTOLINIUM | | | | | | | | | | | | | | | | | | | |
| 1. H.B. | 121 | 95 | 89 | 89 | 93 | | 453 | 283 | 475 | 354 | 432 | | .27 | .34 | .19 | .25 | .22 | | 50 |
| 2. E.T. | 118 | 99 | 77 | 76 | 78 | | 629 | 450 | 552 | 626 | 559 | | .19 | .22 | .14 | .12 | .14 | | 50 |
| 3. A.F. | 140 | 92 | 78 | 86 | 81 | | 739 | 621 | 902 | 956 | 1445 | | .19 | .15 | .09 | .09 | .06 | | 50 |
| 4. L.H. | 145 | 81 | 62 | 76 | 92 | | 853 | 492 | 41 | 1076 | 1151 | | .17 | .16 | ... | .07 | .08 | | 25 |
| 5. G.C. | 151 | 103 | 95 | 102 | 111 | | 815 | 537 | 774 | 789 | 648 | | .19 | .19 | .12 | .13 | .17 | | 25 |
| 6. V.M. | 166 | 113 | 90 | 91 | 85 | | 209 | 137 | 104 | 113 | 124 | | .79 | .82 | .87 | .81 | .69 | | 37.5 |
| 7. S.L. | 122 | 77 | 66 | 59 | 57 | | 1475 | 490 | 702 | 1448 | 540 | | .08 | .16 | .09 | .04 | .11 | | 12.5 |
| 8. O.H. | 145 | 123 | 103 | 106 | 111 | | 1262 | 1003 | 913 | 1063 | 906 | | .11 | .12 | .11 | .10 | .12 | | 37.5 |
| Mean | 139 | 98 | 83 | 86 | 89 | | 804 | 502 | 558 | 803 | 726 | | .25 | .27 | .23 | .20 | .20 | | |
| Per cent of control | | 71 | 60 | 62 | 64 | | | 62 | 69 | 100 | 90 | | | 108 | 92 | 80 | 80 | | |
| P Value* < | | .001 | .001 | .001 | .001 | | | .05 | .10 | NS°° | NS°° | | | .20 | .20 | .05 | .05 | | |

Key to abbreviations in Table 2A:

C = Control
$D_1$ = 0 to 30 minutes
$D_2$ = 1 hour
$D_3$ = 2 hours
$D_4$ = 3 hours
° = NE: response to norepinephrine (average two 10-minute periods)
°° = NS = P > 0.30

* = $t = \bar{x}\sqrt{\frac{n\,(n-1)}{Sx^2}}$ using C (Control) as the reference point

[d] = Using $D_4$ for comparison

** = Mean blood pressure, direct arterial manometry

† = Renal blood flow = $\frac{\text{Renal plasma flow in ml./minute}}{1-\text{hematocrit}}$

‡ = RVR = Renal vascular resistance = $\frac{\text{Mean blood pressure}}{\text{Renal blood flow}}$

TABLE 2B.—EFFECT OF PENTOLINIUM ON GLOMERULAR FILTRATION RATE AND RENAL PLASMA FLOW COMPARING CONTINUOUS INFUSION WITH SINGLE INJECTION IN PATIENTS WITH HYPERTENSION

periods)

°° = NS = P > 0.30

‡ = RVR = Renal vascular resistance = $\frac{\text{Mean blood pressure}}{\text{Renal blood flow}}$

TABLE 2B.—EFFECT OF PENTOLINIUM ON GLOMERULAR FILTRATION RATE AND RENAL PLASMA FLOW COMPARING CONTINUOUS INFUSION WITH SINGLE INJECTION IN PATIENTS WITH HYPERTENSION

| | *Glomerular Filtration Rate ml./min.* | | | | | | *Renal Plasma Flow ml./min.* | | | | | | *Filtration Fraction* | | | | | | *Hematocrit* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Patient* | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *NE°* | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *NE°* | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *NE°* | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *NE°* |
| *Group A* | | | | | | | | | | CONTINUOUS INFUSION | | | | | | | | | | | | | | |
| 1. L.H. | 101 | 67 | 16 | 7 | 22 | 69 | 464 | 300 | 44 | 53 | 144 | 979 | .22 | .22 | .36 | .13 | .15 | .07 | 39 | 38 | 38 | 34 | 35 | 36 |
| 2. A.McD. | 26 | 27 | 20 | 12 | 14 | 27 | 115 | 117 | 88 | 75 | 84 | 152 | .23 | .23 | .23 | .16 | .17 | .18 | 44 | 45 | 45 | 42 | 43 | 42 |
| 3. L.B. | 45 | 46 | 37 | 37 | 51 | 53 | 168 | 168 | 135 | 139 | 184 | 211 | .27 | .27 | .27 | .27 | .28 | .25 | 41 | 41 | 41 | 36 | 36 | 36 |
| 4. M.T. | 85 | 62 | 71 | 62 | 73 | 100 | 489 | 346 | 569 | 480 | 523 | 551 | .17 | .18 | .12 | .13 | .14 | .18 | 38 | 36 | 36 | 36 | 36 | 36 |
| 5. M.Y. | 77 | 26 | 55 | 55 | 59 | 74 | 387 | 163 | 448 | 390 | 408 | 433 | .20 | .16 | .12 | .14 | .14 | .17 | 42 | 41 | 40 | 40 | 40 | 40 |
| 6. S.L. | 115 | 92 | 66 | 78 | 53 | 127 | 469 | 398 | 293 | 313 | 317 | 486 | .25 | .23 | .23 | .25 | .17 | .26 | 42 | 41 | 41 | 40 | 40 | 40 |
| 7. L.M. | 109 | 130 | 125 | 103 | 113 | 104 | 356 | 395 | 433 | 508 | 319 | 310 | .31 | .33 | .29 | .20 | .35 | .34 | 42 | 42 | 41 | 41 | 41 | 36 |
| 8. G.R. | 66 | 55 | 35 | 46 | 46 | ... | 296 | 266 | 191 | 277 | 275 | ... | .22 | .21 | .18 | .17 | .17 | ... | 34 | 34 | 32 | 32 | 30 | ... |
| Mean | 78 | 63 | 53 | 50 | 54 | 79 | 343 | 269 | 275 | 279 | 282 | 446 | .23 | .23 | .23 | .18 | .20 | .21 | 40 | 40 | 39 | 38 | 38 | 38 |
| Per cent of control | | 81 | 68 | 64 | 69 | 101 | | 78 | 80 | 81 | 82 | 130 | | 100 | 100 | 78 | 87 | 91 | | 100 | 98 | 95 | 95 | 95 |
| P Value* < | | .20 | .10 | .05 | .05 | NS | | .10 | .20 | NS°° | .20 | .20 | | NS°° | NS°° | .01 | .05 | .05 | | .20 | .05 | .001 | .001 | .01 |
| P Value* < [d] | | | | | | .10[d] | | | | | | .20[d] | | | | | | NS[d] | | | | | | .30[d] |
| *Group B* | | | | | | | | | | SINGLE INJECTION | | | | | | | | | | | | | | |
| 1. H.B. | 81 | 49 | 84 | 89 | 84 | | 263 | 164 | 280 | 209 | 255 | | .31 | .30 | .30 | .43 | .33 | | 42 | 42 | 41 | 41 | 41 | |
| 2. E.T. | 67 | 53 | 57 | 70 | 64 | | 390 | 279 | 337 | 388 | 358 | | .17 | .19 | .17 | .18 | .18 | | 38 | 38 | 39 | 38 | 36 | |
| 3. A.F. | 90 | 44 | 82 | 88 | 91 | | 414 | 348 | 514 | 545 | 838 | | .22 | .13 | .16 | .16 | .11 | | 44 | 44 | 43 | 43 | 42 | |
| 4. L.H. | 105 | 29 | 7 | 39 | 91 | | 529 | 305 | 27 | 710 | 748 | | .20 | .10 | .26 | .05 | .12 | | 38 | 38 | 34 | 34 | 35 | |
| 5. G.C. | 87 | 53 | 64 | 75 | 60 | | 497 | 333 | 480 | 489 | 421 | | .18 | .16 | .13 | .15 | .14 | | 39 | 38 | 38 | 38 | 35 | |
| 6. V.M. | 34 | 21 | 14 | 15 | 20 | | 136 | 92 | 71 | 77 | 84 | | .25 | .23 | .20 | .19 | .24 | | 35 | 33 | 32 | 32 | 32 | |
| 7. S.L. | 112 | 51 | 19 | 45 | 23 | | 767 | 255 | 365 | 753 | 286 | | .15 | .20 | .05 | .06 | .08 | | 48 | 48 | 48 | 48 | 47 | |
| 8. O.H. | 123 | 112 | 93 | 101 | 124 | | 757 | 602 | 566 | 638 | 580 | | .16 | .19 | .16 | .16 | .21 | | 40 | 40 | 38 | 40 | 36 | |
| Mean | 87 | 52 | 53 | 65 | 70 | | 469 | 297 | 330 | 476 | 446 | | .21 | .19 | .18 | .17 | .18 | | 41 | 40 | 39 | 39 | 38 | |
| Per cent of control | | 60 | 61 | 75 | 80 | | | 63 | 70 | 101 | 95 | | | 90 | 86 | 81 | 86 | | | 98 | 95 | 95 | 93 | |
| P Values* < | | .01 | .05 | .10 | .20 | | | .05 | .20 | NS°° | NS°° | | NS°° | .20 | NS°° | .20 | | | | NS°° | .20 | .20 | .001 | |

Key to abbreviations in Table 2B:

C = Control
$D_1$ = 0 to 30 minutes
$D_2$ = 1 hour
$D_3$ = 2 hours
$D_4$ = 3 hours
° = NE = Response to norepinephrine (average of two 10-minute periods)

°° = NS = P > 0.30

* = $t = \bar{x}\sqrt{\frac{n(n-1)}{Sx^2}}$ — [d] using period $D_4$ for comparison rather than control value

Filtration fraction = $\frac{\text{Glomerular filtration rate}}{\text{Renal plasma flow}}$

of maximum reduction, which was about the same as the blood pressure reduction obtained in the group of patients receiving pentolinium. This was associated with a moderate reduction in renal blood flow ($p<0.05$) which remained somewhat depressed throughout the study until norepinephrine was given and the blood pressure increased to the control levels again. Then renal blood flow returned to control levels. Associated with the reduction in blood pressure, glomerular filtration rate was depressed to a significant degree ($p<0.01$). This was accompanied by a reduction in urine volume ($p<0.01$) and sodium excretion ($p<0.001$) quite similar to the patients who received pentolinium. All of these functions remained depressed through the period of blood pressure reduction but increased towards control levels when the blood pressure was increased with norepinephrine. Initially, the depression in potassium excretion was also great enough to be statistically significant. As with the patients who received pentolinium, as the infusion of the

TABLE 2C.—EFFECT OF PENTOLINIUM OF WATER AND INFUSION WITH SINGLE INJECTION

| *Patient* | *Age* | *Race* | *Sex* | *Urine Volume ml./min.* C | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *NE°* | *Urine Sodium μEq./min.* C | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *NE°* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Group A* | | | | | | | | | | CONTINUOUS INFUSION | | | | | |
| 1. L.H. | 46 | C | F | 3.5 | 1.3 | 0.3 | 0.2 | 0.7 | 1.1 | 264 | 208 | 38 | 7 | 10 | 275 |
| 2. A.McD. | 50 | C | M | 2.2 | 1.3 | 0.8 | 0.3 | 0.4 | 0.9 | 108 | 96 | 25 | 12 | 8 | 17 |
| 3. L.B. | 44 | C | M | 1.7 | 1.3 | 0.8 | 1.1 | 0.9 | 1.2 | 136 | 62 | 20 | 15 | 16 | 18 |
| 4. M.T. | 42 | C | F | 1.4 | 1.4 | 1.0 | 0.7 | 0.6 | 1.1 | 196 | 115 | 66 | 55 | 63 | 225 |
| 5. M.Y. | 49 | C | F | 9.1 | 0.7 | 0.9 | 1.1 | 1.0 | 1.2 | 625 | 22 | 28 | 28 | 47 | 64 |
| 6. S.L. | 67 | C | M | 10.4 | 5.8 | 2.5 | 6.2 | 0.1 | 2.7 | 645 | 594 | 99 | 71 | 165 | 441 |
| 7. L.M. | 67 | C | M | 1.3 | 2.5 | 6.2 | 0.7 | 0.6 | 0.6 | 186 | 183 | 156 | 37 | 31 | 21 |
| 8. G.R. | 39 | C | F | 4.3 | 4.4 | 2.7 | 0.8 | 0.6 | ... | 181 | 151 | 87 | 51 | 47 | ... |
| Mean | 51 | | | 4.2 | 2.3 | 1.9 | 1.4 | 0.6 | 1.3 | 293 | 179 | 65 | 35 | 48 | 152 |
| Per cent of control | | | | | 55 | 45 | 33 | 14 | 31 | | 61 | 22 | 12 | 16 | 52 |
| P Value* < | | | | | .20 | .20 | .05 | .05 | .10 | | .20 | .05 | .01 | .01 | .10 |
| P Value* <[d] | | | | | | | | | .20[d] | | | | | | .20[d] |
| *Group B* | | | | | | | | | | RESPONSE TO SINGLE INJECTION | | | | | |
| 1. H.B. | 26 | C | M | 0.7 | 0.7 | 1.0 | 0.6 | 0.6 | | 124 | 54 | 119 | 94 | 84 | |
| 2. E.T. | .. | .. | F | 2.9 | 2.2 | 0.5 | 0.6 | 0.4 | | 256 | 151 | 90 | 77 | 58 | |
| 3. A.F. | 54 | C | M | 10.2 | 3.8 | 0.5 | 0.3 | 0.4 | | 117 | 43 | 83 | 92 | 135 | |
| 4. L.H. | 44 | C | F | 6.9 | 0.5 | 0.1 | 0.3 | 0.6 | | 296 | 183 | 89 | 10 | 19 | |
| 5. G.C. | 59 | C | F | 8.8 | 2.8 | 0.8 | 0.9 | 0.9 | | 672 | 129 | 113 | 134 | 149 | |
| 6. V.M. | 39 | W | F | 12.0 | 4.0 | 0.6 | 0.6 | 0.5 | | 1023 | 304 | 7 | 9 | 14 | |
| 7. S.L. | 44 | C | F | 3.3 | 2.7 | 0.1 | 0.4 | 0.2 | | 280 | 264 | 7 | 11 | 8 | |
| 8. O.H. | 44 | C | F | 6.8 | 4.6 | 0.6 | 0.5 | 0.6 | | 709 | 431 | 93 | 81 | 96 | |
| Mean | 44 | | | 6.5 | 2.7 | 0.5 | 0.5 | 0.5 | | 435 | 195 | 75 | 64 | 70 | |
| Per cent of control | | | | | 42 | 8 | 8 | 8 | | | 45 | 17 | 15 | 16 | |
| P Value* < | | | | | .05 | .01 | .01 | .01 | | | .05 | .05 | .05 | .05 | |

Key to abbreviations in Table 2C:
C = Control
$D_1$ = 0 to 30 minutes
$D_2$ = 1 hour
$D_3$ = 2 hours
$D_4$ = 3 hours
° = NE = Response to norepinephrine (average of two 10-minute periods)

ganglionic blocking agent hexamethonium continued, there was a slow and progressive reduction in plasma sodium and potassium concentrations.

**Discussion.** The response to pentolinium administered by continuous intravenous infusion to patients with hypertension as compared to the single injection is presented graphically in Figs. 1A and 1B. It is apparent that the eventual degree of blood pressure reduction is finally the same by both methods of drug administration but that the maximum reduction is obtained much more quickly following the single intravenous injection. This would be expected since the maximum blood concentration of pentolinium is obtained more quickly when the drug is given as a single dose. The effect on glomerular filtration rate and renal blood flow follows the same initial pattern as the reduction in mean blood pressure. However, after a single intravenous injection, the glomerular filtration rate begins to increase within 2 hours after drug administration and renal blood flow has returned to the

ELECTROLYTE EXCRETION COMPARING CONTINUOUS
IN PATIENTS WITH HYPERTENSION

| *Urine Potassium μEq./min.* | | | | | | *Plasma Sodium mEq./L.* | | | | | | *Plasma Potassium mEq./L.* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *NE°* | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *NE°* | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *NE°* |
| **Continuous Infusion** | | | | | | | | | | | | | | | | | |
| 72 | 24 | 17 | 10 | 75 | 128 | 134 | 134 | 134 | 128 | 128 | 128 | 4.2 | 4.2 | 4.2 | 4.2 | 4.2 | 3.6 |
| 63 | 91 | 53 | 38 | 55 | 97 | 139 | 139 | 135 | 135 | 133 | 133 | 5.4 | 5.4 | 5.1 | 5.1 | 5.0 | 5.1 |
| 65 | 52 | 43 | 51 | 64 | 74 | 141 | 141 | 137 | 137 | 137 | 137 | 4.2 | 4.5 | 3.9 | 3.9 | 3.9 | 3.9 |
| 19 | 20 | 42 | 39 | 47 | 55 | 134 | 134 | 134 | 134 | 134 | 134 | 4.3 | 4.4 | 4.4 | 3.6 | 3.2 | 3.3 |
| 90 | 35 | 115 | 115 | 96 | 258 | 141 | 141 | 141 | 141 | 141 | 141 | 4.6 | 4.6 | 4.3 | 4.3 | 3.6 | 5.0 |
| 86 | 87 | 52 | 108 | 67 | 63 | 136 | 136 | 127 | 125 | 125 | 125 | 3.9 | 3.9 | 2.8 | 2.8 | 3.5 | 3.5 |
| 70 | 92 | 93 | 65 | 63 | 57 | 134 | 130 | 127 | 130 | 130 | 131 | 5.5 | 5.1 | 4.7 | 4.4 | 4.1 | 3.9 |
| 30 | 28 | 22 | 30 | 36 | ... | 141 | 143 | 140 | 140 | 139 | ... | 4.5 | 4.4 | 4.2 | 4.2 | 4.0 | ... |
| 62 | 54 | 55 | 57 | 63 | 105 | 138 | 137 | 134 | 134 | 133 | 133 | 4.6 | 4.6 | 4.2 | 4.1 | 3.9 | 4.0 |
| | 87 | 89 | 92 | 102 | 169 | | 99 | 97 | 97 | 96 | 96 | | 100 | 91 | 89 | 85 | 87 |
| | NS°° | NS°° | NS°° | NS°° | .20 | | NS°° | .05 | .05 | .05 | .20 | | .30 | .05 | .05 | .01 | .10 |
| | | | | | .20[d] | | | | | | NS[d] | | | | | | NS[d°°] |
| **Response to Single Injection** | | | | | | | | | | | | | | | | | |
| 59 | 48 | 71 | 73 | 58 | | 139 | 137 | 137 | 137 | 138 | | 4.8 | 4.9 | 4.4 | 4.8 | 4.2 | |
| 32 | 29 | 50 | 44 | 39 | | 135 | 135 | 135 | 135 | 134 | | 4.3 | 4.3 | 4.3 | 4.2 | 3.9 | |
| 65 | 41 | 51 | 51 | 55 | | 130 | 130 | 130 | 130 | 130 | | 5.1 | 5.0 | 5.0 | 4.9 | 4.4 | |
| 36 | 9 | 3 | 57 | 87 | | 144 | 138 | 138 | 135 | 135 | | 3.9 | 3.7 | 3.6 | 3.5 | 2.9 | |
| 35 | 32 | 97 | 60 | 57 | | 139 | 130 | 130 | 130 | 130 | | 4.7 | 4.7 | 4.7 | 4.3 | 3.4 | |
| 122 | 53 | 33 | 39 | 39 | | 133 | 130 | 130 | 129 | 129 | | 4.0 | 3.7 | 3.1 | 3.0 | 3.0 | |
| 44 | 25 | 17 | 34 | 16 | | 136 | 136 | 133 | 132 | 132 | | 4.8 | 4.8 | 4.3 | 3.8 | 3.7 | |
| 95 | 201 | 122 | 228 | 185 | | 134 | 134 | 134 | 131 | 132 | | 5.2 | 5.2 | 4.8 | 4.6 | 3.8 | |
| 61 | 55 | 56 | 73 | 67 | | 136 | 134 | 133 | 132 | 133 | | 4.6 | 4.5 | 4.3 | 4.1 | 3.7 | |
| | 90 | 92 | 120 | 110 | | | 99 | 98 | 97 | 98 | | | 98 | 93 | 89 | 80 | |
| | NS°° | NS°° | NS°° | NS°° | | | .30 | .05 | .05 | .05 | | | .10 | .05 | .01 | .001 | |

°° = NS = $P > 0.30$

* = $t = \bar{x}\sqrt{\frac{n(n-1)}{Sx^2}}$ — [d] using period $D_4$ for comparison rather than control value

C = Negro
F = Female
M = Male

TABLE 3A.—RENAL HEMODYNAMIC RESPONSE TO A CONTINUOUS INFUSION OF HEXAMETHONIUM IN PATIENTS WITH HYPERTENSION

| Patient | Mean Blood Pressure mm. Hg | | | | | | Renal Blood Flow‡ ml./min. | | | | | | Renal Vascular Resistance‡ | | | | | | Total Dose mg. in 3 Hours |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | NE | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *NE* | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *NE* | |
| 1. L.S. | 151 | 136 | 104 | 102 | 120 | 169 | 790 | 851 | 914 | 810 | 782 | 697 | .19 | .16 | .11 | .13 | .15 | .24 | 160 |
| 2. E.B. | 147 | 123 | 109 | 104 | 102 | 148 | 576 | 408 | 529 | 591 | 539 | 670 | .26 | .30 | .21 | .18 | .19 | .22 | 175 |
| 3. M.W. | 127 | 116 | 103 | 90 | 96 | 146 | 849 | 479 | 494 | 686 | 624 | 1206 | .15 | .24 | .21 | .13 | .15 | .12 | 100 |
| 4. K.T. | 140 | 125 | 113 | 117 | 106 | ... | 495 | 431 | 475 | 476 | 416 | ... | .28 | .29 | .24 | .25 | .25 | ... | 81 |
| 5. L.P. | 109 | 74 | 88 | 69 | 76 | 93 | 1200 | 515 | 1095 | 660 | 718 | 947 | .09 | .14 | .08 | .10 | .11 | .10 | 40 |
| 6. O.A. | 158 | 135 | 123 | 120 | 118 | 149 | 349 | 320 | 308 | 266 | 228 | 213 | .45 | .42 | .40 | .45 | .52 | .70 | 300 |
| 7. L.M. | 111 | 102 | 68 | 70 | 83 | 120 | 1105 | 310 | 16 | 107 | 416 | 1115 | .10 | .33 | 4.25 | .65 | .20 | .11 | 70 |
| 8. M.H. | 111 | 75 | 54 | 56 | 87 | ... | 635 | 300 | 77 | 16 | 484 | ... | .17 | .25 | .70 | 3.50 | .18 | ... | 50 |
| Mean | 132 | 111 | 95 | 91 | 99 | 138 | 750 | 452 | 489 | 452 | 526 | 808 | .21 | .27 | .78 | .67 | .22 | .25 | |
| Per cent of control | | 84 | 72 | 69 | 75 | 105 | | 60 | 65 | 60 | 70 | 108 | | 129 | 371 | 319 | 105 | 119 | |
| P Value† < | | .01 | .01 | .001 | .001 | NS | | .05 | .20 | .10 | .05 | NS | | .30 | NS | NS | NS | NS | |
| P Value* < | | | | | | .001 | | | | | | .10 | | | | | | NS | |

| Patient | Glomerular Filtration Rate‡ ml./min. | | | | | | Renal Plasma Flow‡ ml./min. | | | | | | Hematocrit | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *NE* | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *NE* | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *NE* |
| 1. L.S. | 82 | 70 | 51 | 57 | 74 | 78 | 529 | 570 | 640 | 583 | 555 | 495 | 33 | 33 | 30 | 28 | 29 | 29 |
| 2. E.B. | 66 | 51 | 59 | 65 | 52 | 82 | 380 | 269 | 365 | 408 | 372 | 462 | 34 | 34 | 31 | 31 | 31 | 31 |
| 3. M.W. | 95 | 50 | 47 | 63 | 53 | 108 | 518 | 292 | 311 | 432 | 393 | 760 | 39 | 39 | 37 | 37 | 37 | 37 |
| 4. K.T. | 73 | 56 | 68 | 63 | 59 | ... | 272 | 237 | 271 | 276 | 233 | ... | 45 | 45 | 43 | 42 | 44 | ... |
| 5. L.P. | 121 | 43 | 92 | 60 | 69 | 106 | 660 | 283 | 602 | 376 | 395 | 521 | 45 | 45 | 45 | 43 | 45 | 45 |
| 6. O.A. | 42 | 40 | 34 | 35 | 28 | 27 | 206 | 189 | 194 | 165 | 153 | 143 | 41 | 41 | 37 | 38 | 33 | 33 |
| 7. L.M. | 67 | 30 | 5 | 6 | 17 | 52 | 652 | 183 | 10 | 65 | 254 | 658 | 41 | 41 | 37 | 39 | 39 | 41 |
| 8. M.H. | 62 | 31 | 7 | 5 | 52 | ... | 394 | 186 | 48 | 10 | 300 | ... | 38 | 38 | 38 | 38 | 38 | ... |
| Mean | 76 | 46 | 45 | 44 | 51 | 76 | 451 | 276 | 305 | 239 | 332 | 507 | 40 | 40 | 37 | 37 | 37 | 36 |
| Per cent of control | | 61 | 59 | 58 | 67 | 100 | | 61 | 68 | 64 | 74 | 112 | | 100 | 93 | 93 | 93 | 90 |
| P Value† < | | .01 | .01 | .01 | .01 | NS | | .05 | .20 | .10 | .20 | NS | | NS | .01 | .001 | .05 | .10 |
| P Value* < | | | | | | .05 | | | | | | .10 | | | | | | NS |

C = Control observations, average of three 10-minute periods

$D_1$ = Observations made first 30 minutes after infusion started; average of three 10-minute periods

$D_2$ = Observations from one hour after infusion started; average of two 10-minute periods

$D_3$ = Observations made 2 hours after infusion started; average of two 10-minute periods

$D_4$ = Observations made 3 hours after infusion started; average of

NE = Observations made after blood pressure increased with norepinephrine; average of two 10-minute periods

† = $t = \frac{}{x}\sqrt{\frac{n(n-1)}{Sx^2}}$

* = P Value using $D_4$ for comparison rather than control period

‡ = See Table 2 A for key to abbreviations

$D_2$ = Observations from one hour after infusion started; average of two 10-minute periods

$D_3$ = Observations made 2 hours after infusion started; average of two 10-minute periods

$D_4$ = Observations made 3 hours after infusion started; average of three 10-minute periods

† = $t = \bar{x}\sqrt{\frac{n(n-1)}{Sx^2}}$

* = P Value using $D_4$ for comparison rather than control period

‡ = See Table 2 A for key to abbreviations

TABLE 3B.—EFFECT OF CONTINUOUS INFUSION OF HEXAMETHONIUM ON WATER AND ELECTROLYTE EXCRETION IN PATIENTS WITH HYPERTENSION

| | | | | *Urine Volume ml./min.* | | | | | | *Sodium Excretion μEq./min.* | | | | | | *Potassium Excretion μEq./min.* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Patient* | *Age* | *Race* | *Sex* | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *NE* | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *NE* | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *NE* |
| 1. L.S. | 49 | C | F | 12.1 | 10.1 | 4.1 | 0.7 | 0.8 | 4.7 | 314 | 199 | 93 | 93 | 100 | 675 | 39 | 32 | 26 | 32 | 30 | 67 |
| 2. E.B. | 58 | C | F | 4.8 | 2.1 | 1.6 | 1.6 | 0.6 | 3.4 | 516 | 340 | 296 | 273 | 98 | 480 | 45 | 31 | 65 | 77 | 33 | 119 |
| 3. M.W. | 37 | C | F | 5.1 | 1.6 | 0.4 | 0.4 | 0.3 | 1.8 | 94 | 33 | 11 | 10 | 10 | 321 | 94 | 47 | 43 | 62 | 54 | 168 |
| 4. K.T. | 51 | C | M | 13.6 | 8.9 | 2.2 | 2.2 | 1.1 | ... | 466 | 374 | 306 | 357 | 156 | ... | 78 | 65 | 84 | 131 | 70 | ... |
| 5. L.P. | 61 | C | F | 8.4 | 1.3 | 0.9 | 0.5 | 0.6 | 5.9 | 130 | 21 | 34 | 14 | 15 | 39 | 39 | 17 | 64 | 38 | 37 | 64 |
| 6. O.A. | 52 | C | F | 4.6 | 2.6 | 1.8 | 1.9 | 0.6 | 0.4 | 496 | 364 | 271 | 262 | 80 | 83 | 100 | 118 | 122 | 113 | 85 | 82 |
| 7. L.M. | 51 | C | F | 0.5 | 0.3 | 0.1 | 0.2 | 0.2 | 1.7 | 47 | 35 | 9 | 10 | 10 | 82 | 86 | 44 | 8 | 11 | 39 | 135 |
| 8. M.H. | 65 | C | F | 8.0 | 1.8 | 0.1 | 0.1 | 0.4 | ... | 127 | 65 | 36 | 36 | 45 | ... | 27 | 12 | 3 | 5 | 31 | ... |
| Mean | 53 | | | 7.1 | 3.6 | 1.4 | 1.0 | 0.6 | 3.0 | 274 | 179 | 132 | 132 | 64 | 280 | 64 | 46 | 52 | 59 | 47 | 106 |
| Per cent of control | | | | | 51 | 20 | 14 | 8 | 42 | | 65 | 48 | 48 | 23 | 102 | | 72 | 81 | 92 | 73 | 166 |
| P Value† < | | | | | .01 | .01 | .01 | .01 | .10 | | .001 | .001 | .01 | .01 | NS | | .05 | NS | NS | .05 | .05 |
| P Value* < | | | | | | | | | .05 | | | | | | .10 | | | | | | .10 |

| | *Plasma Concentration Sodium mEq./L.* | | | | | | *Plasma Concentration Potassium mEq./L.* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *NE* | *C* | $D_1$ | $D_2$ | $D_3$ | $D_4$ | *NE* |
| Mean (8 patients) | 136 | 133 | 133 | 133 | 132 | 133 | 4.9 | 4.5 | 4.5 | 4.5 | 4.5 | 4.4 |
| Per cent of control | | 98 | 98 | 98 | 97 | 98 | | 92 | 92 | 92 | 92 | 90 |
| P Value† < | | .05 | .05 | .10 | .01 | .10 | | .20 | .30 | .10 | .20 | .01 |
| P Value* < | | | | | | NS | | | | | | NS |

Key to abbreviations:

C–$D_4$ = See Table 3A

NE = See Table 3A

NS = See Table 3A

† = $t = \bar{x}\sqrt{\frac{n(n-1)}{Sx^2}}$

* = P Value using $D_4$ for comparison rather than C

control level by this time. But when the continuous infusion is maintained, there is no tendency for renal blood flow or glomerular filtration rate to return toward the control levels. The urine volume and sodium excretion are depressed by both routes of administration and remain depressed throughcut the study. The onset of reduced excretion rates is much more rapid after the single injection method of drug administration as compared to a continuous infusion. Blood pressure reduction did not have a significant effect on potassium excretion by either route of drug administration.

In Figs. 2A and 2B, the response of the hypertensive patients and the normotensive subjects are compared following the adminisration of pentolinium by continuous infusion. The blood pressure was reduced for the group of hypertensive patients to approximately a normotensive level whereas in the

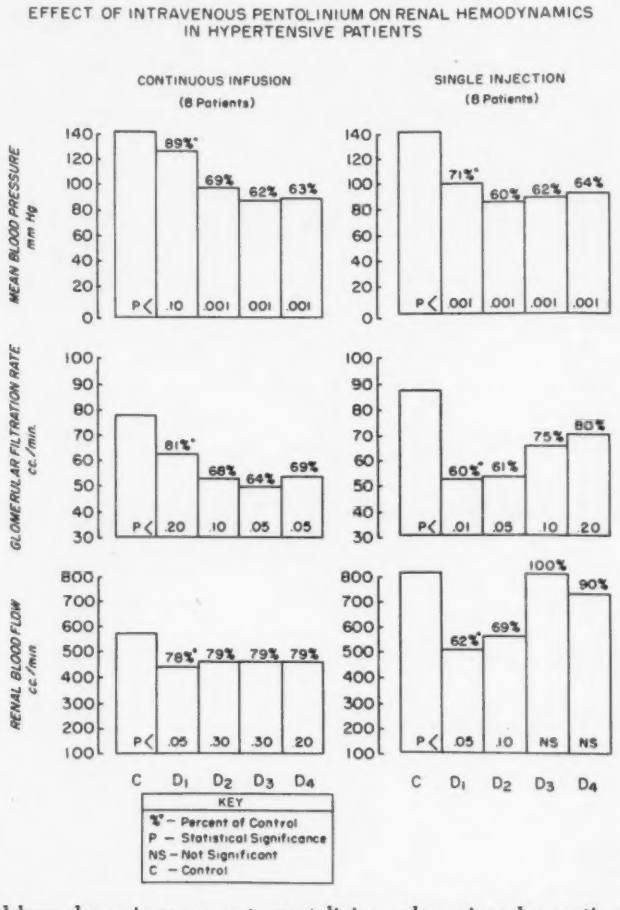
EFFECT OF INTRAVENOUS PENTOLINIUM ON RENAL HEMODYNAMICS IN HYPERTENSIVE PATIENTS
CONTINUOUS INFUSION (8 Patients)
SINGLE INJECTION (8 Patients)
MEAN BLOOD PRESSURE mm Hg
GLOMERULAR FILTRATION RATE cc./min.
RENAL BLOOD FLOW cc./min.
89%* 69% 62% 63%
P< .10 .001 .001 .001
71%* 60% 62% 64%
P< .001 .001 .001 .001
81%* 68% 64% 69%
P< .20 .10 .05 .05
60%* 61% 75% 80%
P< .01 .05 .10 .20
78%* 79% 79% 79%
P< .05 .30 .30 .20
62%* 69% 100% 90%
P< .05 .10 NS NS
C D1 D2 D3 D4
KEY
%* – Percent of Control
P – Statistical Significance
NS – Not Significant
C – Control

Fig. 1A.—Renal hemodynamic response to pentolinium when given by continuous intravenous infusion as compared to single injection.

normotensive subjects, the blood pressure was reduced to hypotensive levels (Fig. 2A). Despite the fact that the blood pressure only approximated the normotensive range in the patients with essential hypertension, glomerular filtration rate was reduced to 64% of the control level and renal blood flow to 78%, both of which were statistically significant. This was contrasted with the normotensive group by a reduction of glomerular filtration rate to 73% of the control value initially and after stabilization to 83 and 85% of the control levels. At the same time, renal blood flow was initially reduced to 76% of control and stabilized at 86 to 89%. These observations indicate that in the hypertensive patients, when the blood pressure is reduced to normotensive levels acutely, renal vasodilatation is not adequate to maintain renal blood flow and glomerular filtration rate. In fact, the normal kidney is able to produce a greater vasodilatation at hypotensive levels than is the hypertensive

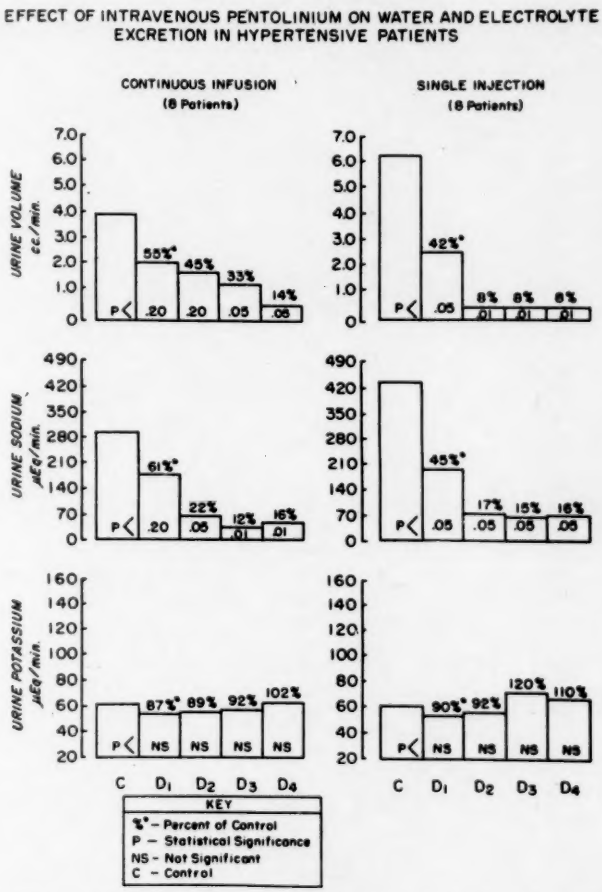


Fig. 1B.—Comparison of effect on water and electrolyte excretion.

kidney at normotensive levels of blood pressure. The reduction in urine volume and sodium excretion after maximum reduction in blood pressure has been about the same in both the normotensive subjects (Fig. 2B) and the hypertensive patients. Both groups showed a reduction for the group except that onset of action may be more rapid with hexamethonium. Likewise, the degree of depression of glomerular filtration rate is also comparable except that the initial depression appeared more rapidly with hexamethonium. The mean

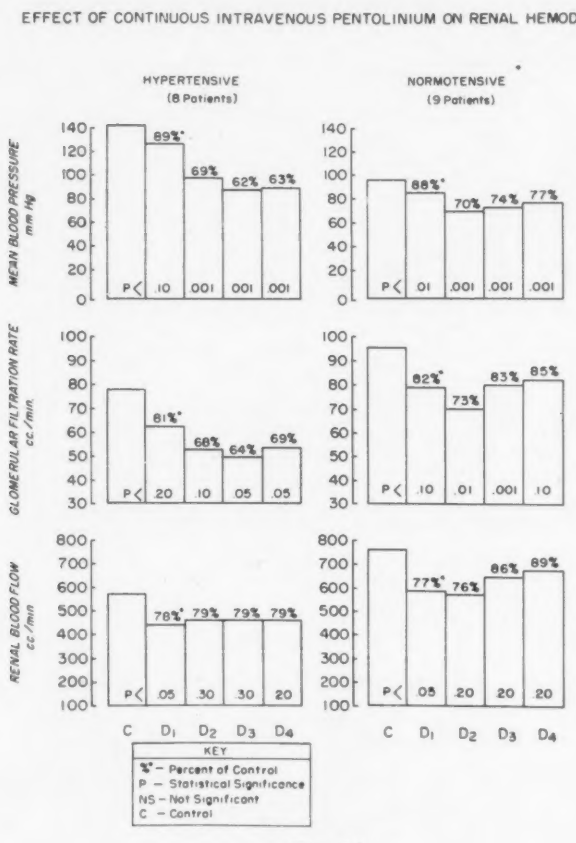
EFFECT OF CONTINUOUS INTRAVENOUS PENTOLINIUM ON RENAL HEMODYNAMICS
HYPERTENSIVE (8 Patients)
NORMOTENSIVE (9 Patients)
MEAN BLOOD PRESSURE mm Hg
GLOMERULAR FILTRATION RATE cc/min.
RENAL BLOOD FLOW cc/min
89%* 69% 62% 63%
P< .10 .001 .001 .001
88%* 70% 74% 77%
P< .01 .001 .001 .001
81%* 68% 64% 69%
P< .20 .10 .05 .05
82%* 73% 83% 85%
P< .10 .01 .001 .10
78%* 79% 79% 79%
P< .05 .30 .30 .20
77%* 76% 86% 89%
P< .05 .20 .20 .20
C D1 D2 D3 D4
KEY
%* – Percent of Control
P – Statistical Significance
NS – Not Significant
C – Control

Fig. 2A.

marked retention of both sodium and water.

Figures 3A and 3B compare the results with a continuous infusion of pentolinium as compared to a continuous infusion of hexamethonium in patients with hypertension. It will be noticed that there is very little difference in the degree of blood pressure blood pressure and glomerular filtration rates were depressed and remained depressed throughout the study as long as the infusions of pentolinium or hexamethonium were continued. The reduction in glomerular filtration rate was associated with a parallel reduction in water and sodium excretion (Fig. 3B) although the depression of sodium ex-

cretion tended to be greater following the administration of pentolinium. However, when the values are contrasted statistically, there was a significant reduction in sodium and water excretion for both drugs but there was no statistically significant difference between the drugs. There was usually some depression in potassium excretion but usually this was not great. These observations lead to the conclusion that the degree of blood pressure reduction is similar with hexamethonium as compared to pentolinium. Although the dose requirement of pentolinium is considerably less than the dose of hexamethonium, the renal hemodynamic response is the same.

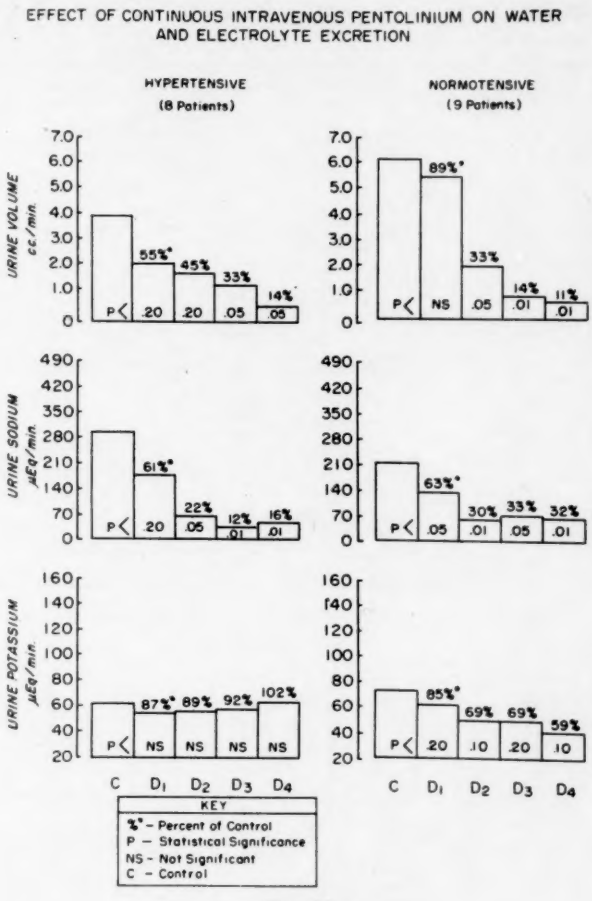


Fig. 2B.

Fig. 2.—Comparison of hypertensive patients with normotensive subjects; (2A) effect of continuous intravenous infusion of pentolinium on renal hemodynamics, (2B) effect of continuous infusion of pentolinium on water and electrolyte excretion.

**Summary and Conclusions.** The renal effects of pentolinium administered by continuous intravenous infusion have been studied in 8 patients

with hypertension and 9 patients with normal blood pressure. The drug was also studied following a single intravenous injection to 8 patients with hypertension. The observations obtained following continuous intravenous infusion to hypertensive patients continuous infusions. However, after one hour, the renal hemodynamic effects were similar irrespective of the method of drug administration. However after 2 to 3 hours, the glomerular filtration rate and renal blood flow were returning towards the control levels

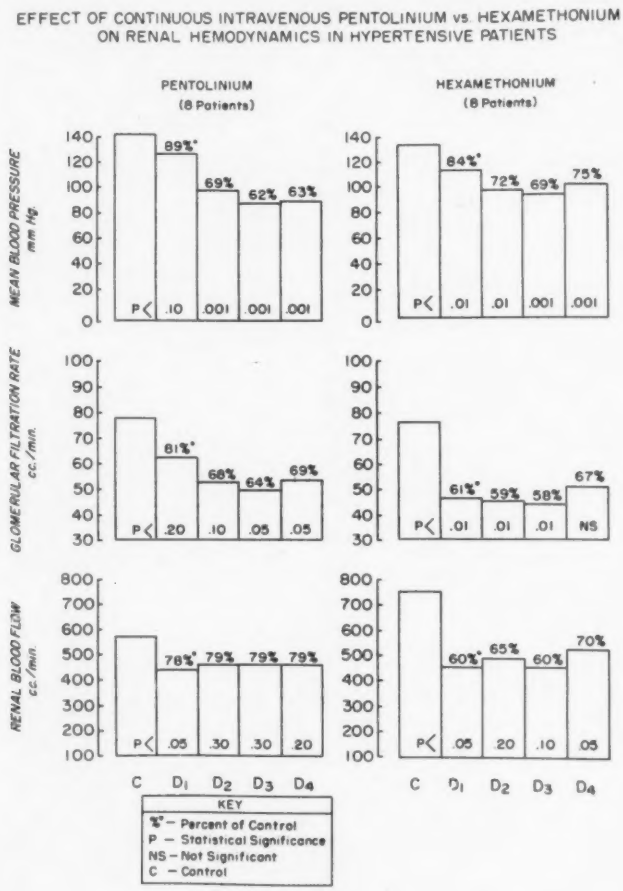
EFFECT OF CONTINUOUS INTRAVENOUS PENTOLINIUM vs HEXAMETHONIUM ON RENAL HEMODYNAMICS IN HYPERTENSIVE PATIENTS
PENTOLINIUM (8 Patients)
HEXAMETHONIUM (8 Patients)
MEAN BLOOD PRESSURE mm Hg
GLOMERULAR FILTRATION RATE cc./min.
RENAL BLOOD FLOW cc./min.
89%* 69% 62% 63%
P< .10 .001 .001 .001
84%* 72% 69% 75%
P< .01 .01 .001 .001
81%* 68% 64% 69%
P< .20 .10 .05 .05
61%* 59% 58% 67%
P< .01 .01 .01 NS
78%* 79% 79% 79%
P< .05 .30 .30 .20
60%* 65% 60% 70%
P< .05 .20 .10 .05
C D1 D2 D3 D4
KEY
%* – Percent of Control
P – Statistical Significance
NS – Not Significant
C – Control

Fig. 3A.

were compared with those made on a similar group of patients who received hexamethonium by continuous intravenous infusion.

The onset of action was much more rapid following single intravenous injections of pentolinium than during following single intravenous injections but remained depressed to about the same degree as the initial depression during the continuous intravenous infusions.

Associated with the reduction in glomerular filtration rate and renal

blood flow, there was a similar and parallel reduction in sodium and water excretion. There was some reduction in potassium excretion but this was usually not statistically significant. the blood pressure was reduced to hypotensive levels.

There was no significant difference between the renal hemodynamic response to blood pressure reduction with

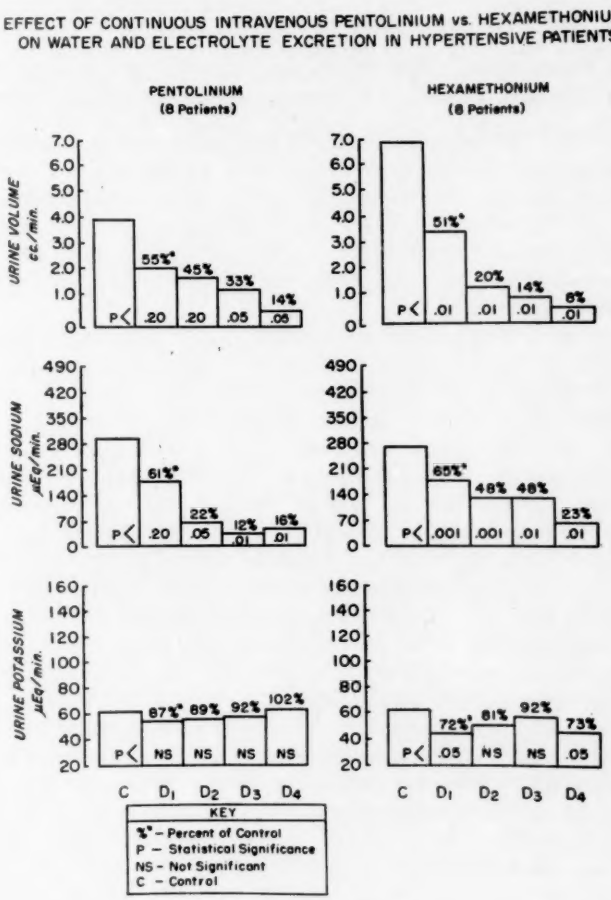


Fig. 3B.

Fig. 3.—Comparison of pentolinium with hexamethonium; (3A) renal hemodynamic response, (3B) effect on water and electrolyte excretion.

These alterations of renal hemodynamics and water and electrolyte excretion rates in the hypertensive patients occurred within a normotensive range and were greater than those observed in the normotensive subjects in whom pentolinium as compared to hexamethonium when both drugs were given by continuous infusions. Likewise, the depression in water and electrolyte excretion following intravenous infusions of these drugs was similar.

REFERENCES

1. **Freis, E. D., Partenope, E. A., Lilienfield, L. S.,** and **Rose, J. C.:** Circulation, **9,** 540, 1954.
2. **Mills, L. C.,** and **Moyer, J. H.:** Am. J. Med. Sci., **226,** 1, 1953.
3. **Moyer, J. H.,** and **Mills, L. C.:** J. Clin. Invest., **32,** 172, 1953.
4. **Smirk, F. H.:** New England Med. J., **52,** 1, 1953.

## SUMMARIO IN INTERLINGUA

### Le Effecto de Pentolinium Super le Hemodynamica Renal e le Excretion de Aqua e del Electrolytos: Un Comparation con Hexamethonium

Le effectos renal de pentolinium administrate per continue infusion intravenose esseva studiate in 8 patientes con hypertension e 9 patientes con normal pression de sanguine. Le droga esseva etiam studiate post un sol injection intravenose in 8 patientes con hypertension. Le observationes obtenite post le continue infusion intravenose in patientes hypertensive esseva comparate con le observationes obtenite ab un simile gruppo de patientes qui recipeva hexamethonium per continue infusion intravenose.

Le declaration del effecto esseva multo plus rapide post unic injectiones intravenose de pentolinium que in infusiones continue. Tamen, post un hora le effectos hemodynamic renal esseva simile, sin reguardo a qual methodo de administration esseva usate. Post 2 a 3 horas, le valores del filtration glomerular e del fluxo de sanguine renal comenciava retornar verso le nivellos de controlo in le caso del unic injectiones intravenose. In le caso del continue infusion intravenose, ille valores remaneva deprimite a circa le grado de lor depression initial.

Associate con le reduction del valores de filtration glomerular e del fluxo de sanguine renal, il habeva un deduction simile e parallel in le valores del excretion de natrium e aqua. Un certe reduction de excretion de kalium esseva etiam notate, sed in general isto non esseva statisticamente significative. Iste alterationes del valores hemodynamic renal e del valores del excretion de aqua e electrolytos in patientes hypertensive occurreva intra le limites normotensive. Illos esseva plus marcate que le correspondente alterationes observate in individuos normotensive in qui le pression sanguinee esseva reducite a nivellos hypotensive.

Nulle differentia significative esseva constatate inter le responsas hemodynamic renal al reduction del pression sanguinee per medio de pentolinium e per medio de hexamethonium quando ambe drogas esseva administrate per infusion continue. Etiam le depression del excretion de aqua e electrolytos post infusiones intravenose esseva simile pro le duo drogas.

# THE RELATION BETWEEN APPEARANCE AND BEHAVIOR OF THE ISLANDS OF LANGERHANS IN MAN*

By Francis D. W. Lukens, M.D.

and

W. Wallace Dyer, M.D.

(From the George S. Cox Medical Research Institute, University of Pennsylvania, Philadelphia, Pennsylvania)

Is there any relation between the structure of the islands and their functional capacity? Pathology as practiced at the necropsy table has left many questions about diabetes unanswered. The use of the biopsy as applied to many other diseases has been largely neglected in the case of diabetes. The reasons for this are obvious. The pancreas is not readily available for biopsy and there are few situations in which a striking change in diabetes may take place. In the absence of gross disease, biopsy of the pancreas, when the organ is exposed at operation, is usually a simple and safe procedure. In experimental diabetes and in the rare instances of diabetes associated with adrenal tumors, one finds circumstances in which the function of the islands may be tested in a striking manner. Sections of the pancreas preceding the production of experimental diabetes and sections from human biopsies will be examined in the light of what the remaining islands were able to do after the sections were taken.

One may begin by considering the islands of Langerhans of a normal rat. This species is not made diabetic by growth hormone[5], but is quite susceptible to alloxan[12]. The rat develops severe but temporary diabetes from large doses of corticotrophin or cortisone[5,10]. No matter how long the adrenal hormones are given, no matter how long the hormonal imbalance and hyperglycemia are continued, these islands do not develop hydropic degeneration[6]. They have considerable capacity for hyperplasia[2,6]. When the administration of adrenal hormones is stopped and even when it is continued, the glycosuria disappears and the animal does not become permanently diabetic. The islands of the rat cannot hypertrophy enough to compensate for the gross destruction caused by alloxan or 95% pancreatectomy, but, even then, the islands which remain appear to maintain their structure.

The islands of a normal cat may next be considered. Omitting technical details, they will be described as morphologically similar to those of the rat. However, the cat cannot be made diabetic with cortisone[1] and it is extremely resistant to alloxan[12]. In this species, partial pancreatectomy, or the administration of growth hormone[1,5], or massive injections of glucose[3], readily produce hyperglycemia. Under all of these conditions, the islands, unlike those of the rat, undergo degranulation, hydropic degeneration and ultimately atrophy[3]. Permanent diabetes is the result.

Table 1 summarizes the differences

*Modified from a presentation before the American Clinical and Climatological Association, November, 1955.

in the behavior of these two species. The diabetogenic activity of growth hormone or corticotrophin is largely, if not entirely, extrapancreatic in nature. The difference between the activity of these hormones in these animals probably has nothing to do with the islands. On the other hand, the last three lines of Table 1 are direct responses of the islands. The similarity of appearance and the marked differences in the behavior of the islands in these two animals should stimulate the labors of laboratory investigators.

What is known of the behavior of the islands of Langerhans in man? The lesions at necropsy have been studied and the insulin content and changes in granulation[19] have been described. There is little knowledge of the islands in man in the earlier periods of the diabetic patient's life. The biopsies of 3 persons, whose diabetes was associated with disorders of the adrenal glands, will illustrate the difficulty of correlating appearance and behavior of this organ in man.

TABLE 1.—RESPONSES OF TWO SPECIES TO DIABETOGENIC PROCEDURES

| *Observation* | *Rat* | *Cat* | |
|---|---|---|---|
| Diabetes from growth hormone | No (5) | Yes (1, 5) | Extra- |
| Diabetes from ACTH or cortisone | Yes (5, 10) | No (1) | pancreatic |
| Diabetes from alloxan | Yes (12) | No (?) (12) | |
| $\beta$ cells breakdown (hydropic, etc.) | No (6) | Yes (3) | Insular |
| Island hyperplasia | Marked (2, 6) | Slight (?) (3) | |

Figure 1*A* shows an island of Langerhans from a nondiabetic patient. This normal island is presented for comparison with the sections taken from diabetic patients. Figure 1*B* illustrates an island of a 43-year-old woman, whose history has been briefly reported[13]. She had mild diabetes for one year and needed 15 units of insulin daily on a maintenance diet. On this regimen she had a slightly elevated morning blood sugar, usually about 160 mg. per 100 ml., before her operation. The operation was performed to remove a pheochromocytoma, which had caused typical symptoms for 5 years. At operation the biopsy of the pancreas (Fig. 1*B*) showed marked degranulation or early hydropic degeneration of the beta cells. After operation she recovered from her diabetes as indicated by an entirely normal glucose tolerance test 6 months after she left the hospital. The point is that these are islands of a patient who recovered completely when the metabolic stress of the medullary tumor was removed.

Figure 2*A* is from the pancreas of H.S., a woman who also had diabetes and a pheochromocytoma. She was 67 years old and diabetes had been diagnosed 4 years before this section was taken. At first her diabetes was controlled by diet, then insulin was needed when hyperthyroidism developed. After treatment of this complication with radio-iodine, insulin was stopped. About one year before operation she began to have the symptoms of adrenal medullary hypersecretion which included paroxysmal hypertension and increasing glycosuria. Shortly before operation, treatment with insulin was resumed and 50 units daily were required to control the diabetes at that time. At operation in December, 1954, a medullary tumor of the left adrenal was removed and this section was taken. This operation was followed by relief of her symptoms and a return of the blood pressure to normal, events

which indicated that there were no multiple or accessory tumors. Her diabetes improved so that she was managed without insulin, but her glucose tolerance test was still grossly abnormal.

not cured like the first patient (A.S.). The islands of H.S. showed less morphological change than the islands of A.S. who recovered.

Figure 2*B* shows an island of a 53-year-old woman (A.P.) who had Cushing's syndrome, for which bilateral adrenalectomy was performed. The section of the pancreas was taken at the time of the second adrenalectomy. Symptoms and findings of Cushing's syndrome developed rapidly in March,

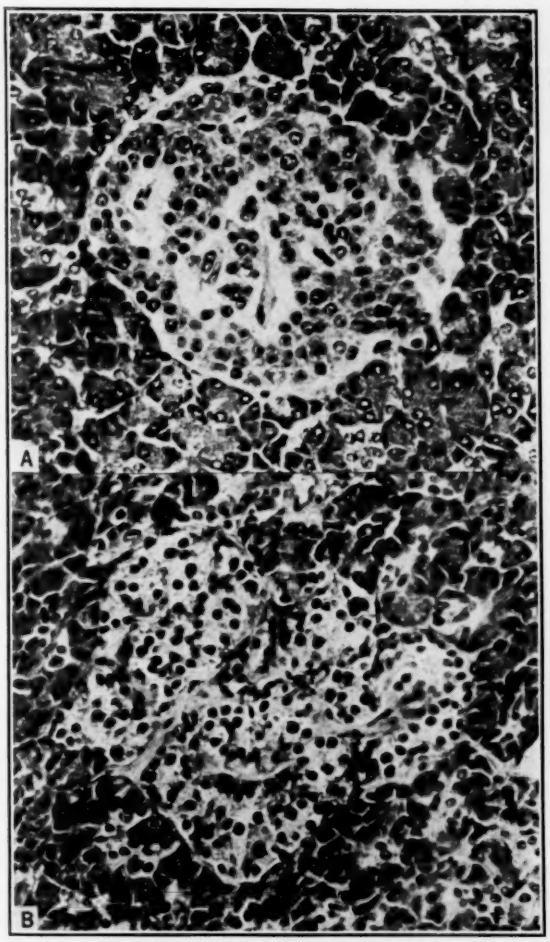


Fig. 1.—*A.* Normal human island of Langerhans. *B.* Island of A.S. Note pale cytoplasm of early hydropic degeneration and pyknotic nuclei. Gomori stain × 290.

In summary, a mild diabetic, whose disease was exaggerated once by hyperthyroidism and once by a pheochromocytoma, was restored to her originally mild diabetic state by the removal of an adrenal tumor but was

1955, and in May, 1955, she was found to have diabetes for which she was given a diet and 50 units of insulin daily. In the Hospital of the University of Pennsylvania she was first controlled on a diet of protein 70, fat 70 and carbohydrate 140 gm., and 50 units of insulin, daily. On June 26, the right adrenal was removed. After this the dose of insulin was gradually reduced to 20 units daily even with slight fever. This improvement is greater than one might expect from unilateral adrenalectomy and such a course often follows adequate insulin dosage of several weeks' duration. In any case, both factors were present.

On July 12, left adrenalectomy and pancreatic biopsy were performed. Postoperatively there was slight drainage from the wound which was attributed to the pancreatic biopsy. Her postoperative febrile reaction was less severe than usual but lasted for 2 weeks. She was discharged on the following regimen: A diet of protein 100,

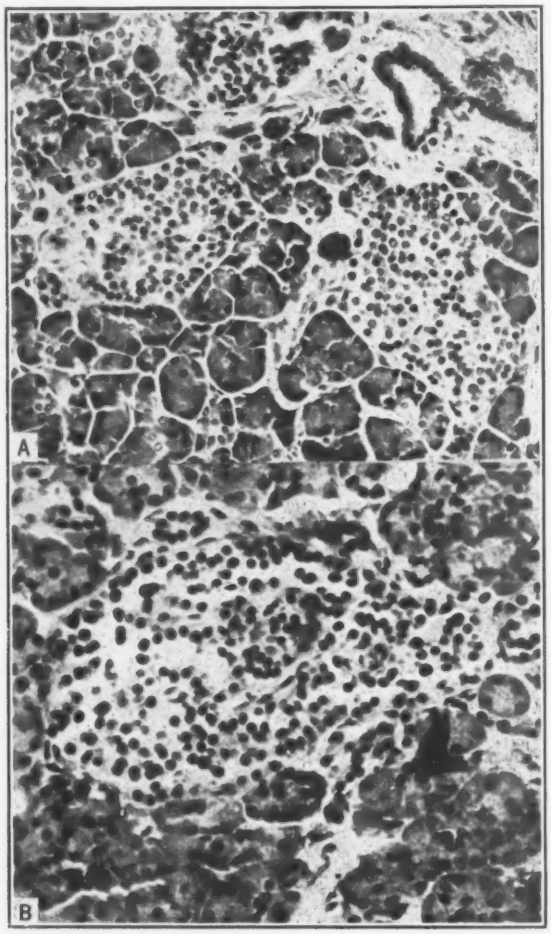


Fig. 2.—*A.* Islands of H.S. H & E × 230. *B.* Island of A.P. H & E × 290.

fat 100, carbohydrate 260; 50 mg. cortisone daily and 4 gm. enteric coated salt tablets; and 10 units of NPH insulin daily. For the last 5 days in the hospital she was free of glycosuria on this regimen.

The island shown in Fig. 2*B* was regarded as normal in appearance on direct microscopic examination. The same section contained an island in advanced hyaline degeneration and a large ill-defined island which was considered typical of hyperplasia. This mixed histological appearance in one small sample of tissue from this patient is related to the following principal events: a) the reduction in insulin requirement by diet and insulin in a diabetic treated within 4 months of the diagnosis of the disease[14]; b) the removal of one and later of both adrenals; c) a final need for some insulin on a diet which the writers consider unduly large, and a maintenance dose of cortisone. In view of the appearance of the islands, it is our opinion that cells which appear to be unlikely to improve (contrast Fig. 1*B*) have been relieved of a large metabolic burden. The nondiabetic ought to tolerate the diet and dose of cortisone which she is taking, so that she has not recovered in spite of this demonstrable improvement.

**Discussion.** Examination of a few of the reported cases of diabetes and pheochromocytoma (Table 2) shows that such persons may or may not recover from diabetes. There is no relation between the known duration or the severity of the diabetes before operation and its postoperative course. In such patients one ought to distinguish between the improvement in diabetes and the so-called recovery from diabetes. We have used the reduction in insulin requirement and the reversal to normal of the sugar tolerance test as criteria of these responses. Such assumptions demand validation by the observation of many more patients for much longer periods of time.

In the case of Cushing's syndrome, Sprague *et al.*[16] reported that: "Of the 10 patients who had frank diabetes before operation, 7 had normal values for fasting blood sugar and no glycosuria after operation." The operations were total or subtotal adrenal resection, and sugar tolerance tests and other details are not available. McCullagh and Alivisatos[15] cite 2 patients with Cushing's syndrome who had "complete clinical recovery following adrenal

TABLE 2.—VARIABLE RESPONSE OF DIABETES AFTER REMOVAL OF PHEOCHROMOCYTOMA

| No. | Patient or Reference | Duration of Diabetes (preop.) | Duration of Observation (postop.) | Insulin Units | | Glucose Tolerance (postop.) |
|---|---|---|---|---|---|---|
| | | | | preop. | postop. | |
| 1 | 4 | 3 yrs. | 5 mos. | 15–25 | 0 | Normal |
| 2 | 8 | 7 mos. | 7 wks. | 10–45 | 0 | " |
| 3 | 17 | 11 mos. | | 40–80 | 0 | " |
| 4 | 17 | ? | 5 wks. | 0 | 0 | See note * |
| 5 | 18 | ? | 6 mos. | 0 ? | 0 | Normal |
| 6 | 9 | 4 yrs. ? | 1 yr. | 36 | 0 | " |
| 7 | A.S. | 11 mos. | 6 mos. | 5–15 | 0 | " |
| 8 | 7 | 3–4 mos. | 10 mos. | 85 | 0 | Abnormal |
| 9 | 11 | ? | 10 yrs. | ? | ? | See note * |
| 10 | H.S. | 4 yrs. | 8 mos. | 0–50 | 0 | Abnormal |

* Tolerance tests not reported: in Case 4, normal blood sugars and in Case 9 an unchanged severity of diabetes, postoperatively.

surgery." Apparently the same possibilities for improvement or recovery of diabetes apply to patients with adrenal cortical hyperfunction.

Like man, animals may show different behavior of the islands at different times. After partial pancreatectomy or during treatment with pituitary extract in dogs and cats, the islands undergo hydropic degeneration and atrophy, but during the subsequent permanent phase of diabetes there may be no progression in the severity of the diabetes even though the hyperglycemia and glycosuria resemble the conditions of the "causative" period.

At the beginning of this report we said that biopsy of the pancreas was a simple and safe procedure. In this connection the records of 68 pancreatic biopsies done in the Hospital of the University of Pennsylvania during the past 20 years have been reviewed. These include the 3 patients reported above. The circumstances under which pancreatic tissue has been taken are suggested by the following arbitrary categories.

A. *Islet cell tumors (suspected or found) and explorations unaccompanied by gross lesions.* This group represents biopsy of the pancreas in the virtual absence of abdominal disease. Of the 68 biopsies, 17 were in this category. In only one, patient A.P. of this report, was there any suggestion of difficulty from the biopsy. Incidentally, the few patients in this group who were closed without drainage appeared to have the most favorable convalescence.

B. *Biopsy incidental to operations on the biliary tract.* Here a relatively undamaged pancreas is sectioned in the presence of other abdominal disease. Regardless of the state of the pancreas, convalescence with biliary drainage is the rule. There were 20 patients in this group. In only one was any complication attributed to pancreatic drainage and this appeared on review to be a small or doubtful component of the complex biliary tract disease.

C. *Biopsy in primary pancreatic disease (necrosis, calculi, cancer, and others).* Thirty-one patients fell in this category of disorders in which operation is difficult and convalescence often prolonged. Tissue sent to the pathologist was usually excised as part of the operation and not as simple biopsy. Hence no complications were attributed to the examination itself.

**Summary.** Biopsies of the pancreas of 3 diabetic patients have been viewed with the subsequent course of the diabetes in mind. After removal of a pheochromocytoma one patient recovered from diabetes; another improved but did not recover. (Recovery here refers to a return of the glucose tolerance test to normal limits.) A third patient improved but still required insulin after total adrenalectomy for Cushing's syndrome. These preliminary observations in man have been compared with those of experimental diabetes in an effort to relate the morphology of the islands to their functional capacity under various conditions.

REFERENCES

1. **Abelove, W. A.,** and **Paschkis, K. E.:** Endocrinology, **55,** 637, 1955.
2. **Abrams, G. D., Baker, B. L., Ingle, D. J.,** and **Li, C. H.:** Ibid., **53,** 252, 1953.
3. **Dohan, F. C.,** and **Lukens, F. D. W.:** Ibid., **42,** 244, 1948.
4. **Duncan, L. E., Semans, J. H.,** and **Howard, J. E.:** Ann. Int. Med., **20,** 815, 1944.
5. **Engel, F. L., Viau, A., Coggins, W.,** and **Lynn, W. S.:** Endocrinology, **50,** 100, 1952.
6. **Friedman, N. B.,** and **Marble, A.:** Ibid., **29,** 577, 1941.
7. **Goldner, M. G.:** J. Clin. Endocrinol., **7,** 716, 1947.
8. **Green, D. M.:** J. Am. Med. Assn., **131,** 1260, 1946.
9. **Griessmann, H.:** Zentralbl. Chir., **77,** 1343, 1952.
10. **Ingle, D. J., Sheppard, R., Evans, J. S.,** and **Kuizenga, M. H.:** Endocrinology, **37,** 341, 1945

11. Joslin, E. P., Root, H. F., White, P., and Marble, A. M.: The Treatment of Diabetes Mellitus, 9th Ed. Philadelphia: Lea & Febiger, 1952, p. 640.
12. Lukens, F. D. W.: Physiol. Rev., **28**, 304, 1948.
13. Idem: Proc. Am. Diabetes Assn., **10**, 103, 1950.
14. Lukens, F. D. W., and Dohan, F. C.: Pennsylvania Med. J., **48**, 24, 1944.
15. McCullagh, E. P., and Alivisatos, J. G.: Diabetes, **3**, 349, 1954.
16. Sprague, R. G., Kvale, W. F., and Priestley, J. T.: J. Am. Med. Assn., **151**, 629, 1953.
17. de Vries A., Rachmilewitz, M., and Schumert, M.: Am. J. Med., **6**, 51, 1949.
18. Wilkins, R. W., Culbertson, J. W., Greer, W. E. R., Halperin, M. H., Litter, J., Burnett, C. H., and Smithwick, R. H.: Tr. Assn. Am. Phys., **62**, 253, 1949.
19. Wrenshall, G. A., Bogoch, A., and Ritchie, R. C.: Diabetes, **1**, 87, 1952.

*(Interlingua on page 337)*

## SUMMARIO IN INTERLINGUA

*(See page 274 for original article)*

### Observationes Additional Super le Effectos Cardiovascular de Lactato de Natrium: Effectos in Subjectos Normal e in Varie Arrhythmias

Le effectos cardiovascular de infusiones de molar lactato de natrium super varie arrhythmias es discutite e comparate con le correspondente effectos super cordes normal. Le serie studiate consisteva de 32 subjectos. Illo includeva subjectos normal e patientes con varie typos de anormalitate myocardial in le presentia de normal rhythmos sinusal, con partial bloco cardiac atrio-ventricular, con bradycardia sinusal, con hypersensibilitate del sinus carotidic, con extrasystoles, e con amplification de QRS, associate con varie factores etiologic (partial e complete bloco cardiac atrio-ventricular e le pulsos idioventricular de arresto cardiac). In le majoritate del subjectos le dose administrate esseva inter 100 e 200 ml con un tempore de infusion de inter 10 e 15 minutas. Le alterationes electrocardiographic esseva ponite in correlation con le sequente datos hematologic: pH, potentia a ligar $CO_2$, acido lactic, e le electrolytos natrium, kalium, e calcium. Alterationes electrocardiographic esseva notate prinicipalmente in subjectos con lente frequentias cardiac occurrente insimul con bradycardia sinusal e partial e complete bloco cardiac atrio-ventricular. Le majoritate de iste patientes monstrava signos de un accelerate frequentia cardiac al culmine del effecto de lactato de natrium. Le alterationes maximal esseva usualmente observate intra alicun minutas post le completion del infusion. Le alterationes del undas T e del segmentos ST que esseva notate in certe casos pareva explicabile como resultato del alterationes electrolytic que occurreva in le corde post le infusion de lactato de natrium.

Iste solution es satis ben tolerate, e pauc manifestationes toxic esseva observate. In 3 subjectos con avantiate morbo cardiac, transiente extrasystoles esseva observate post le infusion. Extrasystoles observate in un altere patiente sin signos evidente de organic morbo cardiac esseva eliminate post le administration de lactato.

In 4 patientes le infusion del lactato molar non resultava in ulle alteration del grado de hypersensibilitate del sinus carotidic.

Le molar lactato de natrium exhibiva un definite tendentia a restringer amplificate complexos QRS associate con partial e complete bloco cardiac atrio-ventricular, bloco de branca, e le pulsos idioventricular de arresto cardiac.

Le mechanismo del effectos clinic e electrocardiographic es discutite. Lor signification clinic es delineate.

# PROGRESS
# OF
# MEDICAL SCIENCE

## PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

G. LYMAN DUFF, M.A., PH.D., F.R.S.C., F.R.C.P.(C)
STRATHCONA PROFESSOR OF PATHOLOGY, McGILL UNIVERSITY

AND

ROGER W. REED, M.A., M.D., C.M.
PROFESSOR OF BACTERIOLOGY AND IMMUNOLOGY, McGILL UNIVERSITY, MONTREAL, CANADA

## RECENT ADVANCES IN THE LABORATORY DIAGNOSIS OF TUBERCULOSIS

BY ROGER W. REED, M.A., M.D., C.M.

AND

O. MORGANTE, M.D., M.SC.
DEPARTMENT OF BACTERIOLOGY AND IMMUNOLOGY, McGILL UNIVERSITY
MONTREAL, CANADA

THE methods used for the laboratory diagnosis of tuberculosis in man have changed very little in the past fifty years. Although the tubercle bacillus was one of the first pathogenic microörganisms to be isolated and studied extensively, we still know comparatively little about the metabolism of the organism. According to Dubos[53] "Primitive bacteriological techniques worked out decades ago for the detection of tubercle bacilli in sputum and other pathological materials are still in use today. Yet it is certain that most bacilli do not survive the barbarous treatment with alkali or acids to which they are submitted during preparation of specimens for the culture test. Moreover, it is also beyond doubt that the empiricism symbolized by the use of egg and serum media constitutes only a crude approximation to conditions which are optimal for bacillary growth."

The observation has frequently been made that the diagnosis of tuberculosis without bacteriologic proof is questionable. For a certain diagnosis the tubercle bacillus must be demonstrated in pathological material from the patient. The problem of doing so is becoming more acute because, as a result of the wider use of mass roentgenographic surveys designed to discover tuberculosis in apparently healthy individuals[23], an increasing proportion of minimal disease is being observed[139]. Therefore, the number of patients in whom it is difficult or impossible to demonstrate the presence of tubercle bacilli by smear or culture is also in-

creasing. Accurate and early bacteriologic diagnosis then becomes increasingly important[211] both to prevent the exposure of healthy individuals to suspected tuberculosis cases and to avoid delay in proper treatment of proven cases, which may result in progression of disease[165].

Microscopic examination of sputum is the most rapid and economical means of demonstrating the presence of tubercle bacilli but is only about 60% efficient in those with all stages of tuberculosis[157]. Examination of smears in those with minimal tuberculosis is much less effective[47,186]. Culture and animal inoculation remain the most reliable methods[186], although the former are deficient in many respects[53]. The constantly increasing number of publications concerning media and methods designed to provide more accurate, more rapid and more reliable laboratory diagnosis of tuberculosis, attest to the fact that at present no one method is entirely satisfactory. Many investigations are in progress to develop more efficient bacteriological techniques as well as reliable serological tests to aid in the diagnosis of human tuberculosis. It is our purpose in this review to discuss briefly some of the developments of the past decade in these fields.

**Cultural Methods.** It has been pointed out by Cummings[43] that the ideal culture medium should support rapid growth of small numbers of tubercle bacilli, should permit easy differentiation by colonial morphology between pathogenic and nonpathogenic acid-fast bacilli, should inhibit growth of contaminants and should be simple to prepare from readily available ingredients. He suggests that Lowenstein-Jensen's medium is the best of present conventional media for routine diagnosis. Shaffer[181] found that the potato medium of Corper and Uyei[41,42] was best because of the simplicity of its preparation and high percentage of positive cultures and that Petragnani's medium[154] was a very close second choice. Schwabacher[178] after comparing a number of conventional media concluded that a simple egg medium, was most suitable for growth of tubercle bacilli. Other large scale comparisons have been made[43,130,187] from which it was concluded that Lowenstein-Jensen's medium is most satisfactory. There is, however, considerable dissatisfaction with conventional types of media used for routine isolation and identification of tubercle bacilli[53].

One of the recent advances in bringing about the rapid growth of tubercle bacilli resulted from the studies of Dubos and his colleagues on the effects of serum albumin, fatty acids and other factors on the growth of tubercle bacilli[46,50,51,52,54,55] which culminated in the development of several culture media designed for specific purposes[56]. Of interest in this review are the fluid and solid media developed specifically for diagnostic purposes. The basal medium in both cases is a buffered electrolyte solution containing casein digest, asparagin, and a mixture of bovine serum albumin Fraction V, oleic acid and Tween 80. Dubos and Middlebrook[56] were able to obtain growth of tubercle bacilli in from 7 to 15 days from pathological material which did not reveal tubercle bacilli on direct microscopic examination. In the fluid medium virulent tubercle bacilli tend to grow in long strands of characteristic serpentine or corded appearance which can readily be identified under the low power after preparing and staining a smear from the medium. It was shown that tubercle bacilli grown in Dubos' fluid medium exhibited a high degree of pathogenicity for rabbits, guinea pigs, mice and chick embryos[158]. While morphology on Dubos' solid medium is somewhat different from that on conventional egg

yolk solid media, virulence is maintained at a high level[136].

Foley[62,63] found that Dubos' fluid media provided almost as high a percentage of positive isolations as did guinea pig inoculation but that colonies on Dubos' solid medium were not sufficently characteristic to permit its use. Another reported difficulty was that saprophytic Mycobacteria could not be easily differentiated from virulent acid-fast organisms. Foley obtained growth in an average of 10.6 days and Goldie[76] reported positive cultures in Dubos' media in from 8 to 14 days. Roberts *et al.*[171] compared Dubos' albumin agar oleic acid medium with several conventional media and concluded that it was superior to these for purposes of diagnostic culture. They also found that both the Dubos' liquid and solid media were somewhat superior to guinea pig inoculations where the specimen contained very small numbers of tubercle bacilli. Foley[63] and Sula[193] were able to demonstrate acid-fast bacilli microscopically after one week's incubation, but there was frequent heavy growth of contaminating bacteria which rendered the negative cultures in Dubos' media of doubtful significance. Konowalchuk and Reed[109] added gentian violet 1:1,000,000 to Dubos' fluid media and found that the dye did not inhibit growth of tubercle bacilli but brought about a very significant reduction in the amount of contamination. However, neither Dubos' fluid nor Dubos' solid media have become widely adopted as diagnostic culture media for a number of reasons. It is necessary to prepare and examine smears from the fluid medium to determine the presence or absence of growth of Mycobacteria. This is a time-consuming operation in a routine laboratory. When the solid medium is used, colony morphology is not typical.

Within the past few years the micro-culture method originally described by Koch[107] for early detection of tubercle bacilli has been re-investigated. By coagulating blood serum, inoculated with material containing tubercle bacilli, and incubating, Koch was able to demonstrate growth of tubercle bacilli within a week, using magnifications of 30 to 40 diameters. Several workers[87,160,216] have studied this culture method utilizing organisms from pure cultures as inoculum. Pryce[160], in 1941, developed a microculture procedure using a medium consisting of citrated blood and water in equal proportions, with which he demonstrated evidence of growth microscopically with low power after one week of incubation. He regarded the method as showing considerable promise but it proved too cumbersome for routine diagnostic use. Rosenberg[173] further modified Pryce's slide culture technique and applied it to the isolation of tubercle bacilli from the sputa of tuberculous patients. He found that 95% of specimens positive on direct smear showed good growth after 6 days which could be observed with low power and that only 3% of these cultures were contaminated.

Berry and Lowry[19,20,121] developed special culture tubes and decontamination tubes which permitted simple and safe handling of sputum smears dried on ordinary microscope slides. Following decontamination with weak sulphuric acid and rinsing with distilled water, slides were incubated horizontally in Kirchner's medium[106] enriched with Fraction V bovine albumin. Slides were removed from the culture medium, fixed, stained and examined microscopically after incubation for up to one week. They found that by the sixth day 90% of the microcolonies were visible under low power. Berry and Lowry's slide culture method proved to be almost as effective as conventional methods on specimens showing a posi-

tive smear of the concentrate but much less effective upon specimens which showed a negative smear. In a later report[21] they found that in the case of gastric washings, slide culture yielded more positives and in the case of sputum fewer positives than routine culture methods. One of the striking things revealed in this study was that slide cultures were positive in an average of 3.5 days, while routine cultures became positive after an average of 37.4 days. During the next 2 years reports appeared on the diagnostic use of slide culture from Chile[206,207], China[32], Czechoslovakia[113], France[7,8,15,16,148], Germany[108], Japan[218], Poland[78] and Sweden[88] which demonstrated its superiority over conventional methods, both in the shorter time required for positive culture and in its technical simplicity. On the other hand, Collard and Mann[37] believed slide culture to be inferior to orthodox methods as did Oeding[146] and others[43,161].

Reed in 1953[162] reported a modification of Berry and Lowry's method which yielded excellent results. Kirchner's medium[106], enriched with pooled sterile human serum instead of bovine albumin, provided much more luxuriant growth of tubercle bacilli, and changes were made in the decontamination and washing procedures. Significantly more slide than conventional cultures became positive on sputum specimens showing a positive smear of concentrate, although in smear-negative specimens there was no appreciable difference between the two culture methods. Fifty per cent more positive cultures were obtained if the slides were incubated for 2 weeks instead of one. Simpson and Reed[183] later described the results of culture of some 2,200 specimens by the slide method and by conventional methods on Herrold's egg yolk agar after concentration. Of the total of 224 specimens with a positive smear of the concentrate, 95% were positive by slide culture, whereas only 72% were positive by routine culture. Seventy per cent of 81 smear-negative specimens were positive by each culture method. Striking contrast was shown between the time required for a positive culture by each method. Fifty-two per cent of slide cultures were positive at the end of one week and 100% at the end of 2 weeks. No routine cultures were positive at the end of 2 weeks, only 39% in 4 weeks and 75% in 7 weeks. A similar comparison[184] of 2,500 additional specimens showed figures identical to the above. Simpson and Reed[185] have also shown on a small number of comparative trials that slide culture is not only superior to five different conventional culture media but that in some instances it appears to be more delicate than guinea pig inoculations as a means of detecting small numbers of tubercle bacilli.

Favorable reports of slide culture continue to appear, primarily in the European literature[13,110,168]. Langenscheidt[114] found that the results of his slide culture method agreed completely with the more time-consuming Petragnani culture technique and that slide culture was much faster and much less expensive. Chaudhuri[31] described a slide culture method in which 50% of cultures were positive in 2 days and 100% positive in 6 days, but concluded that the method should always be supplemented by other culture methods as well as by animal inoculation. Kroger and Bosse[112] indicate the advantage of slide culture in the much shorter time required but feel that macroscopic cultures are indispensable for diagnostic verification. Hedgecock and Faucher[85] have described a slide culture method for primary isolation which they believe to be more delicate and certainly more rapid than conventional methods. Slide culture technique has

been adapted successfully for determining the sensitivity of tubercle bacilli to streptomycin[8,11,13,15,15a,16,37,44,45,74,163,168,176,177,182,207], to isoniazid[13,163,168,191], p-aminosalicylic acid[163,168] and other tuberculostatic substances[8,17,148]. The method has also proved very useful as a research tool for the study of tubercle bacilli[18,110,115].

The advantages of slide culture are the rapidity of growth even from small inocula, the reproducible medium with readily available ingredients, and its technical simplicity. Reed[162] demonstrated that a single technician could culture 50 specimens of sputum completely in 3 hours using this method, since time-consuming concentration procedures are not required. It appears to be more sensitive to small inocula than conventional methods, and there is some evidence to indicate that it is also more sensitive than guinea pig inoculation[185]. One disadvantage of slide culture is that to date no absolutely reliable method has been found to indicate by microscopic examination of colonies whether or not the acid-fast organisms being examined are virulent tubercle bacilli or saprophytic acid-fast bacilli. In the majority of cases, virulent organisms will show characteristic corded colonies[136] microscopically, while saprophytes will show random arrangement of individual cells. However, there are exceptions in both cases.

It has been shown that the chick embryo may be infected with tubercle bacilli by a variety of routes[29,59,140]. Lee *et al.*[118] found that intravenous inoculation resulted in a very uniform degree of infection of chick embryos, producing marked involvement of liver and spleen. This method of infection was used to test the effect of streptomycin and other substances on tubercle bacilli[116,117]. McNelly and Riddell[129] attempted to use chick embryos in the culture of *M. tuberculosis* from pathological specimens. Both chorio-allantoic membranes and yolk sacs were inoculated with material under test, and at the same time Dubos' fluid medium, Petragnani's and Wooley's media and guinea pigs were inoculated. It was found that the lesions on the chorio-allantoic membrane were very evident and could be readily evaluated as to type. The method appeared to be as sensitive as conventional egg slant cultures and provided a convenient method for enrichment prior to animal inoculation. As a routine isolation method, considerable time could be saved in identification, since positive results were secured in from 4 to 7 days. Hsiung and Haley[97] inoculated the yolk sacs of chick embryos with sputum in which tubercle bacilli were present in such small numbers as to give negative smears and cultures. The eggs were then incubated from 7 to 10 days and subcultures of the yolk made on artificial media. Positive cultures became apparent in 2 to 3 weeks. Attempts were made to concentrate the small number of organisms present in the yolk according to the method of Brueck and Buddingh[27] but these were not successful. It would appear that use of embryonated eggs for routine isolation and identification of tubercle bacilli has not yet been developed to the point where it constitutes a useful, simple and rapid procedure.

A number of workers[2,15,36,173] have reported the successful use of blood for the cultivation of tubercle bacilli. Horse[138], human[58,160,216], rabbit[215] and guinea pig blood[87] have been used either alone or combined with a variety of basal media. In 1951, Tarshis and Frisch[65,198] described a blood agar medium which provided growth of tubercle bacilli from small inocula in 10 to 16 days. The medium recommended consisted of blood agar base, hydrated with 1% glycerine and containing 25%

bank blood. They found that defibrinated, citrated or oxalated blood, or bank blood up to 56 days old were all equally capable of initiating growth. This blood agar medium was found to be equal to, and in many cases superior to, several conventional egg media from the standpoint of early detection. In later studies[195,196,200,201] blood agar plus penicillin and malachite green proved satisfactory for the cultivation of tubercle bacilli under routine diagnostic conditions. In their most recent reports Tarshis *et al.*[202,203] presented the results from 4,050 sputum specimens cultured on blood agar-penicillin medium and on Lowenstein-Jensen medium under routine diagnostic conditions. They found that out of 1,515 positive cultures, 94% were positive on blood agar and 90.1% on the Lowenstein-Jensen. Growth appeared on blood agar after an average of 18.5 days and on Lowenstein-Jensen medium after an average of 21.6 days. They point out that the chief advantages of the blood medium are its economy, simplicity of preparation, stability and ability to grow tubercle bacilli from small inocula easily, recognizably and in a short time. Other workers[24,34,94,97,123,164] have confirmed the findings of Tarshis and his colleagues on the usefulness of blood agar medium for the cultivation of *M. tuberculosis* under routine diagnostic conditions. Tarshis *et al.*[197,199] and others[120,123] have used it successfully for determination of the sensitivity of tubercle bacilli to streptomycin and other therapeutic agents. Although cultures do not become positive as quickly as by slide culture, the method warrants further study.

Hirsch[91] has recently developed a charcoal agar of which the essential ingredients are inorganic salts, glycerine, asparagin and activated charcoal, together with casein hydrolysate and cholesterol. Charcoal is used to bind fatty acids which are present in some brands of commercial agar and which are toxic to tubercle bacilli. The medium was developed to replace egg yolk media, since the chemical constitution of these media varies considerably and cannot be readily reproduced. The advantages of the charcoal agar medium over those containing egg or albumin are economy, reproducibility, ready availability of ingredients, ease of preparation and stability to sterilization in the autoclave. This medium supported good growth both of virulent strains of tubercle bacilli and of several strains of BCG. Hirsch[92] found growth stimulating factors in a residue remaining after extraction of egg yolk with organic solvents. The nature of these compounds has not been established, but it is believed that they act at least in part by neutralizing toxicity of the agar for tubercle bacilli. Whalen and Mallmann[214] found that growth stimulation resulting from the presence of charcoal in the medium was almost as great as that effected by bovine serum albumin, and somewhat greater than that offered by human serum. Charcoal agar has not been widely tested as a diagnostic medium, but appears to give results almost equivalent to those on conventional media. The time required for positive culture is somewhat less than that required on conventional media, but does not compare with the rapidity of appearance of positive slide cultures. The medium itself is no simpler to prepare than the serum-enriched Kirchner's medium used for slide culture.

Molecular filter membranes have been used for some time for cultivation of enteric bacteria[205]. These membranes present a matrix of extreme porosity suitable for rapid bacterial growth restricted to the surface as liquid nutrient diffuses by capillarity into the membrane itself. Orlando and

Bolduan[147] in 1953 reported the satisfactory growth of *M. tuberculosis* together with other bacteria and *Fungi imperfecti* on the surface of membrane filters. Wayne[208,210] repeated this work, growing tubercle bacilli on filter membranes placed over solid Lowenstein-Jensen medium. He found that growth of tubercle bacilli could be observed microscopically in 3 days and that by the thirteenth day characteristic macroscopic morphology appeared. Because the colonies tended to wash off the membrane during staining, impression smears made on slides were utilized for microscopic visualization. Virulent strains of tubercle bacilli showed characteristic corded colonies, whereas saprophytes did not. Wayne adapted the neutral red stain technique of Dubos and Middlebrook[57] for observation of colonial morphology and also utilized it as a microscopic virulence test. In a later report Krasnow, Wayne and Salkin[111] described a modification of the neutral red test which they applied to a number of known virulent mammalian tubercle bacilli, all of which were positive both cytochemically and morphologically. Known saprophytes as well as chromogenic and other Mycobacteria of questionable virulence were either neutral-red negative, noncorded or negative in both respects. The authors believed that the use of membrane filters together with neutral-red technique could be a valuable laboratory diagnostic test.

Rogers, Cooke and Meyers[172] adapted membrane filter cultures for the detection of tubercle bacilli in urine and in pleural, peritoneal and cerebrospinal fluids with good quantitative results. Positive cultures were also obtained on mouthwash gargle specimens in a majority of patients with positive sputum cultures. The membrane filter culture method has been proven particularly useful by Morgante and Murray[141] in the isolation of *M. tuberculosis* from cerebrospinal fluid. They were able to demonstrate with this method that tubercle bacilli persist in the cerebrospinal fluid during treatment for as long as 28 weeks in some cases, and recovered tubercle bacilli from cerebrospinal fluid in 35 of 37 cases of tuberculous meningitis. Hawirko and Murray[84] have described an oil partition technique with which they were able to recover completely very small numbers of tubercle bacilli. Pretreated pathological material was thoroughly shaken with different oils. Tubercle bacilli passed into the oil phase, and were recovered on membrane filters after dissolving the oil. Coconut oil was found to be least toxic. However, some vital lipid was removed from the organisms during oil partition which made subsequent culture difficult. This problem has been partially solved by Hannan[82] by addition of various growth factors to cultures of oil-partitioned tubercle bacilli. In all cases[82,84] membrane filters were planted on Reed's serum-enriched medium[162] made semisolid by the addition of 0.3% agar. It would appear that the membrane filter culture technique has sufficient promise for rapid cultural diagnosis and possibly for *in vitro* virulence testing, to justify further detailed experiments and more actual diagnostic trials. Wayne[209] has reported that taxonomic differences in the genus *Mycobacterium* may be distinguished by oil solvent partition techniques. Hoyt *et al.*[96] developed a filter paper culture technique which appears to have no advantages over the membrane filter method.

Mankiewicz in 1954[126] described a very interesting growth factor for *M. tuberculosis* which is produced by *Candida albicans*. Superinoculation of Lowenstein-Jensen slopes with this organism produced marked growth stimulation of tubercle bacilli, particularly

of strains from patients receiving tuberculostatic drugs. The *C. albicans* colonies "trace" colonies of tubercle bacilli. A subsequent report by Mankiewicz[127] showed that of 1,019 specimens of sputum or gastric washings, 153 were positive on routine culture on Lowenstein-Jensen medium while 308 were positive on the same medium superinoculated with *C. albicans*. In the case of 55 resection specimens cultured on Lowenstein-Jensen medium, 37 and 21 respectively were positive with and without added *C. albicans*. A similar growth factor from a strain of *Fungi imperfecti* has been described by Yukischige[221,222]. This important finding is being studied further and should be of great value in studying the bacteriology of patients under treatment and of resected specimens.

**Virulence Tests.** Animal inoculation has been the only routine method for testing the virulence of Mycobacteria until recently. The growth pattern on special media, and reactions with specific chemical substances have been suggested during the last decade as effective techniques for more rapidly detecting the pathogenicity of tubercle bacilli.

Guinea pigs have been the animals routinely employed in clinical laboratories, since they are susceptible to both human and bovine strains. Enhancement of infection may be brought about by treatment of guinea pigs with cortisone[99]. Mice, which proved to be very sensitive animals to tuberculous infection[64,75,79,137,158], have not been adopted as yet for routine laboratory tests, although their use is common in experimental tuberculosis[98]. While animals are undoubtedly useful to confirm the clinical diagnosis, they are not a reliable index of the severity of human tuberculous infection. The virulence of freshly isolated human strains of tubercle bacilli has been frequently tested, and attempts have been made to correlate results from animals with human tuberculous disease. The results obtained by different investigators[14,49,150] indicate that different strains of tubercle bacilli vary in their virulence for animals, and that no definite correlation exists between animal virulence and the severity of human infection.

Middlebrook, Dubos, and Pierce[136], using special media[158], reported that virulent tubercle bacilli grew in "serpentine cords," while nonvirulent bacilli, such as BCG, possess characteristics which are intermediate between fully virulent cord-forming strains and avirulent noncord-forming variants. The studies of Suter and Dubos[194] demonstrate that cord formation is a necessary but not sufficient condition for virulence of tubercle bacilli. Yegian and Kurung[219] enhanced cord formation by adding unheated serum or plasma to Tween-albumin fluid medium, and observed good correlation between the growth pattern of Mycobacteria and pathogenicity for animals. It was concluded, therefore, that "while all cord-formers are not necessarily virulent, all virulent strains are cord-formers." The presence of cord formation by microcolonies is used as a criterion of virulence in slide cultures[162,184,185] and in membrane filter cultures[111,172] of tubercle bacilli. Noll and Bloch[144] have recently determined that the so-called "cord factor" is a mycolic acid ester which can be recovered from the purified wax fraction of tubercle bacilli.

Dubos and Middlebrook[57] observed that virulent tubercle bacilli bind the dye neutral red in alkaline fluid media and stain red, while nonvirulent bacilli do not fix the dye and are yellow like the medium. Hauduroy and Posternak-Gallia[83] confirmed these findings, and Morse *et al.*[142] found the neutral red reaction as satisfactory as, and more practical than, animal inoculation for testing pathogenicity of Mycobacteria.

Richmond and Cummings[170], on the other hand, obtained positive reactions with saprophytic strains of acid-fast bacilli nonpathogenic for animals. Nile blue was used by Desbordes[48] to differentiate virulent from avirulent acid-fast bacilli. In an alkaline medium the former stain blue, and the latter pink. The results by this method did not differ from those obtained by the method of Dubos and Middlebrook[57]. A number of indophenol dyes have also been tested for the detection of virulence, but with considerably less success[35,152,215a,217].

Interest in virulence determinations on tubercle bacilli from clinical specimens has increased with the demonstration that isoniazid-resistant strains are of low virulence for guinea pigs[9,10,39,101,103,134,153,192] although they are virulent for mice[22,77,102] and are cord-formers[40,151]. Middlebrook[133a] and Cohn *et al.*[36a] have shown a lack of catalase activity in strains of human tubercle bacilli which are highly resistant to isoniazid and of attenuated virulence for guinea pigs. However, the clinical significance of *in vivo* and *in vitro* virulence tests is not yet established, and further investigation is required to understand the nature of virulence and its correlation to human tuberculous disease. While the loss of guinea pig virulence by isoniazid-resistant tubercle bacilli is of considerable interest, the fact remains that these bacilli are isolated from patients with still active tuberculosis.

**Serologic Tests.** A variety of reactions have been studied in attempts to provide a reliable serological method for diagnosis of tuberculosis and for evaluation of the degree of activity of the disease. Complement fixation[155,156,157], agglutination[4,189] and the precipitin test[30,143,213] have all been examined in detail but none has found universal acceptance in the diagnosis or prognosis of tuberculosis.

Keogh, North and Warburton[104] found that red blood cells sensitized with bacterial polysaccharides were agglutinated by a serum containing antibody to the corresponding substances. This property of red blood cells found a practical application in the Middlebrook and Dubos[135] hemagglutination reaction to detect minute amounts of circulating tuberculous antibodies. Sheep red blood cells sensitized with an extract of *M. tuberculosis* H37RV were agglutinated by the serum of patients with active pulmonary tuberculosis to a dilution of 1:8 or higher, and by the serum of a patient with miliary disease to a dilution of 1:256. Evidence was given for the specificity of the test. The most important antigens for this reaction were found to be associated with the polysaccharide fraction of tubercle bacilli, but might also be associated with tuberculoproteins. The hemagglutination reaction stimulated a great deal of interest. Although Middlebrook[133] pointed out the limitations of the test, he stated that "the high degree of specificity of the reaction, when a reliable antigen is used and after experience has been obtained in the performance of the test, suggests that a positive reaction at 1:8 or higher dilution of serum is presumptive evidence of disease due to tubercle bacilli or to a *Mycobacterium* very closely related in antigenic structure." It was hoped that the reaction would be of practical value in the diagnosis and prognosis of tuberculosis.

The most widely adopted modification was the substitution of Old Tuberculin for the bacillary extract, and the use of Group O, Rh-negative human red blood cells instead of sheep erythrocytes. Rothbard *et al.*[174] used Lederle's Old Tuberculin (approximately 4 times the normal strength) to sensitize eryth-

rocytes. They found definite correlation between the hemagglutination titer and the course of the disease, and observed very few positive reactions among nontuberculous individuals. It was concluded, therefore, that the hemagglutination test was specific for tuberculosis and valuable for the appreciation of the activity of the disease. Armstrong and Orlicki[6] found no significant difference in results obtained with Lederle Old Tuberculin and Connaught Concentrated Tuberculin while testing known tuberculous sera. Thalhimer and Rowe[204] introduced a slide modification of the hemagglutination test which seemed useful for rapid screening of the negative-reacting sera of a large population, since slide and tube tests gave very similar results.

Smith and Scott[180,188] obtained positive reactions in 80% of 104 patients with active tuberculosis. Almost all cases with grave illness and those with a long history of arrested disease had negative results. Hemagglutinins were observed in nontuberculous patients and in a variety of healthy adults; the majority of these positive agglutinations were correlated with positive tuberculin skin reactions, or with stimulated antibody production induced by the tuberculin test. Sera of tuberculin-negative individuals usually developed a positive hemagglutination after vaccination with BCG, but correlation could not be established between appearance of hemagglutinins and development of a positive skin test. The test was not found valuable in determining the activity of a tuberculous infection. Sohier, Juillard and Trimberger[190] used "Institut Pasteur" precipitated tuberculin as sensitizing antigen, employing a technique slightly different from the original. They obtained positive agglutinations in 20 of 30 tuberculous patients. Eight of the ten negative reactors were very severely ill. Of 130 healthy young adults, 19 showed hemagglutinins in their sera and of these, 12 had a positive tuberculin skin test. The results were considered on the whole to be satisfactory.

Gernez-Rieux and Tacquet[69] compared Sohier's technique with the Middlebrook and Dubos technique, and found the latter to give fewer false positives with normal sera. Using the latter technique for further investigation[68], they observed positive hemagglutination reactions in 77% of active pulmonary patients, and negative reactions in 96% of nontuberculous individuals. Eighty per cent of cattle with extensive tuberculous lesions were also positive. Streptomycin therapy did not influence the hemagglutination results. The reaction was not always positive after BCG vaccination and when present, was transient and not related to the appearance of cutaneous sensitivity to tuberculin. A comparison with the complement fixation test showed the hemagglutination reaction to be more specific, although its specificity is relative because infections produced by different varieties of Mycobacteria cannot be distinguished from each other.

Adcock, Haley and Davey[1] doubted the usefulness of this test for diagnosis and for evaluation of the progress of disease, because of the high percentage of false positive results with normal sera and the low number (54.4%) of positive tests in those with active disease. Similar conclusions were reached by Fleming *et al.*[61], McDerman[128], Bunn *et al.*[28], Howard *et al.*[95] and Hollander *et al.*[93] after careful investigation of the sera from many tuberculous and nontuberculous patients. Hilson and Elek[89], using human "O" Rh negative cells sensitized with a crude polysaccharide fraction instead of Lederle Old Tuberculin, found a titer of 1:8 or higher to be "significantly associated with tuberculosis" but present

in only one-third of their patients. Using the same technique, Maher-Loughnan and Hilson[124] and Armstrong and Lee[5] compared serological results with clinical, radiological and bacteriological findings and did not find hemagglutination sufficiently specific or sensitive for use in diagnosis or prognosis. Nommik and Meakins[145] modified Rothbard's technique and made a prolonged study of children and adults with active pulmonary and nonpulmonary tuberculosis and of nontuberculous individuals. The level of error was considered to be intolerable. A considerable fluctuation in the hemagglutination titer was observed in the same patient, independently of clinical changes in the disease. The sera of 91% of tuberculous meningitis patients showed a significant titer, while the cerebrospinal fluids did not show antibodies. The hemagglutination reaction was considered unreliable for diagnosis of tuberculosis or as an index of progress of the disease, with the exception of tuberculous meningitis cases where the reaction proved to be of great diagnostic value.

Kirby, Burnell and O'Leary[105] used the techniques of Smith and Scott, of Middlebrook and Dubos, and of Rothbard in their investigation. No significant differences in titers were obtained by the three methods. Positive agglutinations at a titer of 1:8 were found in 10% of 251 nontuberculous patients, while they were negative in 10 patients with active tuberculosis. The diagnostic value of the test was doubted because of the high percentage of false positive results, and the reaction was considered of little practical value, since positive sputum was readily obtained from patients with high hemagglutination titers. Young and Leonard[220] found the test valuable only to exclude tuberculosis when negative. A titer of 1:8 or higher was regarded as only suggestive of active disease, since 26.5% of nontuberculous patients showed this titer, as well as 44.2% of arrested cases.

Haley *et al.*[80] studied the hemagglutination response in normal young adults vaccinated with BCG. The antibody response was transient and not correlated with the development of tuberculin skin sensitivity. Anderson and Platou[3] observed a similar transient response in children after tuberculin skin testing. Hemagglutinins were not demonstrable in sera of very advanced cases or in healing tuberculosis. Hentel and Guilbert[86] investigated the sera of tuberculous and nontuberculous patients, using the Scott and Smith technique. A titer of 1:8 or lower was regarded as normal, and a titer of 1:16 or higher as indicative of tuberculous activity. The authors observed a decrease in hemagglutination titers in patients with arrested tuberculosis and found evaluation of the results difficult in cases with questionable activity. The percentage of negative reactions in treated tuberculous patients was higher than in cases who did not receive antibiotics, and it was felt that the negative results could be correlated with the antibiotic treatment.

Levine[119] made some minor modifications to the Middlebrook-Dubos hemagglutination reaction to test the sera of patients with active and arrested Hansen's disease, and those of tuberculous persons. The titers in the active cases of Hansen's disease were significantly higher than in the clinically arrested cases, and much higher than those from patients with active tuberculosis. The immunologic response to antigenic components of the tubercle bacillus in patients with Hansen's disease was marked and distinct. Levine pointed out that the hemagglutination reaction proved that *M. tuberculosis* and *M. leprae* have a common antigen which stimulates the production of specific antibodies in man.

Hinson *et al.*[90] tested the sera of 130 tuberculous patients and of 64 nontuberculous cases. The test was not considered of diagnostic value, since 5% of nontuberculous controls were positive, and many tuberculous patients were negative at different stages of the disease. It was observed that hemagglutinins were present in significant titers when tubercle bacilli are probably multiplying in the lesions. The authors pointed out that results are influenced by the patient's age, the test being more reliable in the 20 to 30 age group. A fall in antibody titer was noticed during streptomycin therapy, and ascribed to a probable decreased antigenic stimulus.

Richardson Jones and Hinson[169] modified the Coombs' antiglobulin reaction using human "O" Rh negative cells, which were first treated with Lederle Concentrated Old Tuberculin and subsequently exposed to the action of tuberculous serum. The original Middlebrook-Dubos hemagglutination reaction was also done on all sera as a control. Sera of cases of active pulmonary tuberculosis, of nontuberculous patients with intrathoracic disease, and of healthy blood donors were tested. The new technique appeared to be more specific, since the incidence of positive results in nontuberculous sera was not high. The correlation between the anatomic extent of pulmonary tuberculosis and the incidence of positive agglutination reactions was striking. The new technique was not influenced by the patient's age. In other respects, the results obtained by the conventional technique compare with those of the antiglobulin modification. The latter brought evidence for the possible existence of two anti-tuberculins, probably of different specificity.

Choremis and Anastasea[33] used the Smith and Scott technique, to study the sera of a large number of pediatric cases of pulmonary and nonpulmonary tuberculosis, tuberculous meningitis and nontuberculous disease. Of 90 children with tuberculous meningitis, 86% had positive hemagglutination tests at a titer of 1:8 or higher related to the degree of activity of the disease. Antibodies were not demonstrable in the cerebrospinal fluids of 30 patients. Of the remaining tuberculous children, only 2.4% showed a negative hemagglutination reaction. Of the 111 nontuberculous children, 109 gave a negative reaction. It was concluded that the hemagglutination reaction was "a useful tool" for the diagnosis of tuberculosis, and that it may be indicative of the degree of activity of the disease.

Middlebrook[132] in 1950 showed that, when complement is added to the system, hemolysis occurs instead of hemagglutination. Independently, Fisher and Keogh[60] made the same observation, when complement was used with the sera of tuberculous or vaccinated cattle. Middlebrook pointed out that hemolysin and hemagglutination titers in positive sera are qualitatively but not quantitatively related. He could not establish whether different antibodies or different antigens adsorbed onto the red cells were responsible for the differences between hemagglutination and hemolysis. Maillard and Gagliardo[125] standardized the hemolytic method for clinical application and claimed that more quantitative results could be obtained with their technique. Rowe, Spain and Childress[175] compared results obtained by the two methods and found no significant difference.

Gernez-Rieux and Tacquet[70] used different types of tuberculin and observed differences in their sensitizing activity. The active antigenic portion for the hemolytic reaction was found to be bound to the polysaccharide fraction of tuberculin. Negative hemolytic reactions were obtained in 87% of 121

nontuberculous people, and a positive reaction at a level of 1:16 or higher was shown in 76% of 208 sera of active tuberculous patients. It was suggested that the hemolytic test might find a practical application for the diagnosis of active tuberculosis.

Hall, Manion and Johnson[81] did hemagglutination and hemolytic reactions on the sera of a number of tuberculous patients and of immunized rabbits. When tuberculous antibodies could not be detected by these methods they devised a hemolytic modification of the indirect Coombs' (developing) method which disclosed the presence of hemolysins in far advanced cases. The hemolytic modification of Coombs' method appeared to be very sensitive and as specific as the hemagglutination and hemolytic reactions.

Lucentini and Boisvert[122] made a comparative study of hemagglutination, hemolytic and complement fixation reactions, using sera from pulmonary and nonpulmonary tuberculous patients and from nontuberculous individuals. They concluded that the hemagglutination reaction is more sensitive than the hemolytic and suggested that the association of both reactions and of the complement fixation might give interesting results for the clinical evaluation of tuberculosis. Gerstl *et al.*[72] tested the sera of nontuberculous persons before tuberculin skin test was performed, and those of 58 patients with active tuberculosis, to ascertain the clinical value of the Middlebrook hemolytic method. Less than 1.5% of 226 nontuberculous individuals gave a positive hemolytic reaction. Two-thirds of the sera from tuberculous patients showed negative hemolytic reactions. Blocking antibodies were not found in active pulmonary cases with negative serologic reactions. Treatment of sheep erythrocytes with Forssman antibody before adsorption with tuberculin did not increase the sensitivity of the test. The negative results in active cases were considered discouraging, and the method was not deemed sufficiently sensitive for detection of small amounts of antibody. It was concluded that a positive test strongly indicates a tuberculous infection, while the absence of hemolysis does not exclude the presence of tuberculosis. Schwartz *et al.*[179] reached the same conclusion.

Mollov and Kott[139] found neither qualitative nor quantitative correlation between hemagglutinins and hemolysins. It was suggested that the antibodies detected by the two methods are different, and that the hemolytic reaction is a more promising test for the detection of tuberculous infection. Rheins *et al.*[167] introduced a drop technique for the hemagglutination and hemolytic reactions with which they tested the sera of rabbits infected with various strains of acid-fast bacilli. They found the technique as sensitive as standard procedures but quicker and more useful for testing small amounts of serum. Pound[159] prepared an aqueous extract from phenol-extracted *M. tuberculosis*, strain P.N. By agglutination and complement fixation tests, three components were shown to be adsorbed onto the surface of sheep red blood cells. Two of the components were predominantly polysaccharides with different chemical and serologic properties. Sheep erythrocytes, sensitized with them, were agglutinated by antibodies present in tuberculous serum. Hemolysis was obtained when complement was added to the sensitized red blood cell system, and gave the most satisfactory basis for titration of antibody to these fractions. Both fractions gave nonspecific hemolysin titers with a significant number of sera from healthy Mantoux-negative persons.

Gaby, Black and Bondi[66] used the Rothbard hemagglutination technique

to compare and to standardize tuberculins and purified protein derivative (PPD). Quantitative and qualitative differences in tuberculous antigens could be demonstrated by hemagglutinin absorption methods. They further investigated the problem of selective hemagglutinin adsorption[67]. Old Tuberculins prepared from seven species of pathogenic and nonpathogenic Mycobacteria were shown to be antigenically different, although both groups contained common antigens.

Boyden[25] enhanced the sensitivity of sheep red blood cells with the use of a suitable concentration of tannic acid. PPD (Weybridge, containing 5% polysaccharide) was employed as the sensitizing antigen. Very small amounts of antibodies could be detected by this method. Meynell[131] studied the antigenic structure of tubercle bacilli, adsorbing the different antigens with normal and tanned red blood cells. Rheins and Thurston[166] demonstrated that successive adsorption of Old Tuberculin with sheep erythrocytes disclosed antibodies in tuberculous sera which were not detected by the usual sensitizing procedures. They also investigated the effect of tanning on the adsorbing capacities of sheep cells for antigens present in Old Tuberclin (Lederle 4 + International Standard) and in Purified Protein Derivative (PPD), Parke & Davis). Lytic antigens were adsorbed equally well from Old Tuberculin by tanned and normal sheep erythrocytes, but tanned cells adsorbed agglutinogens different from those adsorbed by normal cells. The tanning of cells did not alter adsorption of antigens from small quantities of PPD.

Gerstl *et al.*[71,73] were impressed by the number of tuberculous patients with no apparent circulating antibodies. They attempted to unmask antibodies by fractionation of the serum proteins of tuberculous human sera. Fractionation by the cold ethanol method revealed hemagglutinins in 4 of 8 tuberculous sera which were negative by the Middlebrook-Dubos agglutination method. Protein fractions manifesting antibody activity were shown in sera of seven patients, negative in the complement fixation test. Brodhage[26] reviewed the literature and expressed the opinion that the skeptical attitude of many investigators is not due to the reaction itself, but to the use of an antigen not sufficiently effective for the sensitization of the erythrocytes. He concluded that the introduction of the hemagglutination and hemolytic reactions in the serodiagnosis of tuberculosis represents definite progress.

**Summary.** Recent developments in culture techniques for *M. tuberculosis* offer considerable promise for more rapid, more accurate and more dependable laboratory assistance to the clinician in establishing a positive diagnosis of tuberculosis. Charcoal agar, blood agar and serum-enriched fluid medium used for slide culture are more easily and economically prepared and more readily reproducible than the widely used egg-glycerine agars. These three methods together with membrane filter techniques look most promising today. The usefulness of dye virulence tests has not been fully established. The reliability of serological tests as aids to diagnosis and prognosis in human tuberculosis is also in question. These tests, however, are proving very valuable in the study of immunity to tuberculosis and may yet be adaptable as routine laboratory procedures.

REFERENCES

(1) **Adcock, J., Haley, R. R.,** and **Davey, W. N.:** J. Lab. & Clin. Med., **38,** 736, 1951. (2) **Alexander, E. G.:** Proc. Soc. Exper. Biol. & Med., **31,** 1101, 1934. (3) **Anderson, H. W.,** and **Platou, R. V.:** Pediatrics, **8,** 498, 1951. (4) **Arloing, S.,** and **Courmont, P.:** Ztschr. Tuberk., **11,** 116, 1900. (5) **Armstrong, A. R.,** and **Lee, J. H.:** Canad. Med. Assn. J., **69,** 403, 1953. (6) **Armstrong, A. R.,** and **Orlicki, J.:** Canad. J. Med. Technol., **13,** 67, 1951.

(7) **Badoux, J.:** Bull. Soc. vaudoise Sci. Nat., **64,** 479, 1950. (8) Idem: J. Med. Leysin, **29,** 1164, 1950. (9) **Barnett, M., Bushby, S. R. M.,** and **Mitchison, D. A.:** Brit. J. Path., **34,** 568, 1953. (10) **Barry, V. C., Conalty, M. L.,** and **Gaffney, E.:** Lancet, **1,** 978, 1953. (11) **Bekierkunst, A., Mordarski, M.,** and **Szulga, T.:** Pol. Tyg. Lek., **8,** 461, 1953. (12) **Bekierkunst, A.,** and **Szulga, T.:** Ibid., **8,** 817, 1953. (13) Iidem: Schweiz. Ztschr. Allg. Path. Bakt., **17,** 47, 1954. (14) **Bergeron, A.,** and **Lavagne-Mézière:** Rev. Tuberc. (Paris), **14,** 694, 1950. (15) **Bernard, E.,** and **Kreis:** Ibid., **13,** 124, 1949. (15a) Iidem: Ibid., **13,** 737, 1949. (16) Iidem: Ann. Inst. Pasteur, **77,** 653, 1949. (17) Iidem: Ibid., **80,** 87, 1951. (18) Iidem: Presse Méd., **59,** 385, 1951. (19) **Berry, J. W.,** and **Lowry, H.:** Am. Rev. Tuberc., **60,** 51, 1949. (20) Iidem: Am. J. Clin. Path., **20,** 1037, 1950. (21) Iidem: Tr. Nat. Tuberc. Assn., 264, 1950. (22) **Bloch, H., Widelock, D.,** and **Peizer, L. R.:** Am. Rev. Tuberc., **68,** 734, 1953. (23) **Block, R. G.,** and **Tucker, W. B.:** Ibid., **50,** 405, 1944. (24) **Bojalil, L. F.,** and **Llado, H.:** Rev. Mex. Tuberc., **16,** 94, 1955. (25) **Boyden, S. V.:** J. Exper. Med., **93,** 107, 1951. (26) **Brodhage, H.:** Ergebn. Hyg. Bakt., **28,** 123, 1954. (27) **Brueck, J. W.,** and **Buddingh, G. J.:** Proc. Soc. Exper. Biol. & Med., **80,** 589, 1952. (28) **Bunn, P., Drobeck, B., Gino, J.,** and **Adair, C.:** Ann. Int. Med., **37,** 84, 1952.

(29) **Canat, E. H.,** and **Opie, E. L.:** Am. J. Path., **19,** 385, 1943. (30) **Cannon, P. R.,** and **Marshall, C. E.:** J. Immunol., **38,** 365, 1940. (31) **Chaudhuri, A.:** Antiseptic, **51,** 116, 1954. (32) **Ch'I-Huan, C.,** and **Feng-Lien, W.:** Chin. Med. J., **71,** 176, 1953. (33) **Choremis, C. B.,** and **Anastasea, K. N.:** Am. Rev. Tuberc., **70,** 139, 1954. (34) **Clark, M. E.:** Am. J. Clin. Path., **23,** 671, 1953. (35) **Clark, M. E.,** and **Forrest, E. S.:** Am. Rev. Tuberc., **68,** 786, 1953. (36) **Clough, M. C.:** Ibid., **1,** 598, 1917–18. (36a) **Cohn, M. L., Kovitz, C.,** and **Middlebrook, G.:** Ibid., **70,** 641, 1954. (37) **Collard, P. J.,** and **Mann, P. G.:** J. Clin. Path., **6,** 266, 1953. (38) **Coombs, R. R. A., Mourant, A. E.,** and **Race, R. R.:** Brit. J. Exper. Path., **26,** 255, 1945. (39) **Conalty, M. L.:** Irish J. Med. Sci., **331,** 267, 1953. (40) **Conalty, M. L.,** and **Gaffney, E. E.:** Am. Rev. Tuberc., **71,** 799, 1955. (41) **Corper, H. J.,** and **Uyei, N.:** Ibid., **16,** 299, 1927. (42) Iidem: J. Lab. & Clin. Med., **14,** 393, 1929. (43) **Cummings, M. M.:** Am. J. Clin. Path., **21,** 684, 1951. (44) **Cummings, M. M.,** and **Drummond, M. C.:** Am. Rev. Tuberc., **59,** 599, 1949. (45) **Cummings, M. M., Drummond, M. C.,** and **Schwartz, H. B.:** Dis. Chest, **17,** 202, 1950.

(46) **Davis, B. D.,** and **Dubos, R. J.:** Arch. Biochem., **11,** 201, 1946. (47) **Decker, W. P., Ordway, W. H.,** and **Medlar, C. M.:** Am. Rev. Tuberc., **47,** 625, 1943. (48) **Desbordes, J.:** Ann. Inst. Pasteur, **83,** 809, 1952. (49) **Dhayagude, R. G.,** and **Shah, B. R.:** Indian J. Med. Res., **36,** 79, 1948. (50) **Dubos, R. J.:** Proc. Soc. Exper. Biol. & Med., **58,** 351, 1945. (51) Idem: Ibid., **63,** 56, 1946. (52) Idem: J. Exper. Med., **85,** 9, 1947. (53) Idem: Am. Rev. Tuberc., **70,** 391, 1954. (54) **Dubos, R. J.,** and **Davis, B. D.:** J. Exper. Med., **83,** 409, 1946. (55) **Dubos, R. J., Davis, B. D.,** and **Middlebrook, G.:** Am. Rev. Tuberc., **54,** 204, 1946. (56) **Dubos, R. J.,** and **Middlebrook, G.:** Ibid., **56,** 334, 1947. (57) Iidem: Ibid., **58,** 698, 1948. (58) **Dunphy, L.,** and **Fousek, M. D.:** Yale J. Biol. Med., **19,** 1013, 1947.

(59) **Emmart, E. W.,** and **Smith, M. I.:** Pub. Health Rep., **56,** 1277, 1941.

(60) **Fisher, S.,** and **Keogh, E. V.:** Nature (Lond.), **165,** 248, 1950. (61) **Fleming, J. W., Runyon, E. H.,** and **Cummings, M. M.:** Am. J. Med., **10,** 704, 1951. (62) **Foley, G. E.:** Proc. Soc. Exper. Biol. & Med., **62,** 298, 1946. (63) Idem: J. Lab. & Clin. Med., **32,** 842, 1947. (64) **Francis, J.:** Nature (Lond.), **175,** 344, 1955. (65) **Frisch, A. W.,** and **Tarshis, M. S.:** Am. Rev. Tuberc., **64,** 551, 1951.

(66) **Gaby, W. L., Black, J.,** and **Bondi, A., Jr.:** Ibid., **65,** 272, 1952. (67) Iidem: Ibid., **67,** 657, 1953. (68) **Gernez-Rieux, C.,** and **Tacquet, A.:** Presse méd., **58,** 631,

1950. (69) Iidem: Ann. Inst. Pasteur, 78, 550, 1950. (70) Iidem: Ibid., 81, 149, 1951. (71) **Gerstl, B., Davis, W. E., Jr., Kirsh, D., Hollander, A. G., Barbieri, M.,** and **Weinstein, S. B.:** Am. Rev. Tuberc., 72, 345, 1955. (72) **Gerstl, B., Kirsh, D., Andros, E. M., Winter, J. W.,** and **Kidder, L. E.:** Am. J. Clin. Path., 22, 337, 1952. (73) **Gerstl B., Kirsh, D., Davis, W. E., Jr.,** and **Barbieri, M.:** Science, 120, 853, 1954. (74) **Giammalvo, J. T., Natsios, G. A.,** and **Elton, N. W.:** Am. J. Clin. Path., 19, 76, 1949. (75) **Glover, R. E.:** Brit. J. Exper. Path., 25, 141, 1944. (76) **Goldie, H.:** Proc. Soc. Exper. Biol. & Med., 65, 210, 1947. (77) **Goulding, R., King, M. B., Knox, R.,** and **Robson, J. M.:** Lancet, 2, 69, 1952. (78) **Grabiec, S. J.,** and **Sym, E. A.:** Bull. Inst. Mar. Trop. Med. Gdansk, 4, 163, 1952. (79) **Gray, D. F., Park, B. L.,** and **Mattison, M. W.:** Am. Rev. Tuberc. 69, 92, 1955. (80) **Haley, R. R., Davey, W. N., Adcock, J.,** and **Owen, C. R.:** Ibid., 66, 58, 1952. (81) **Hall, W. H., Manion, R.,** and **Johnson, D. W.:** Tr. Chemother. Tuberc., 176, 1951. (82) **Hannan, C. K.:** Unpublished data, 1955. (83) **Hauduroy, P.,** and **Posternak-Gallia, Y.:** Ann. Inst. Pasteur, 77, 91, 1949. (84) **Hawirko, R. Z.,** and **Murray, E. G. D.:** Canad. J. Pub. Health, 45, 208, 1954. (85) **Hedgecock, L. W.,** and **Faucher, I. O.:** Bact. Proc., 98, 1955. (86) **Hentel, W.,** and **Guilbert, G. D.:** J. Lab. & Clin. Med., 39, 426, 1952. (87) **Hesse, E., Meissner, G.,** and **Quast, G.:** Arch. Exper. Path. Pharmak., 135, 82, 1928. (88) **Hesselberg, I.,** and **Oeding, P.:** Acta tuberc. Scandinav., 27, 217, 1952. (89) **Hilson, G. R. F.,** and **Elek, S. D.:** J. Clin. Path., 4, 158, 1951. (90) **Hinson, K. F. W., Richardson Jones, A.,** and **Chamberlin, J. A.:** Brit. J. Tuberc., 46, 50, 1952. (91) **Hirsch, J. G.:** Am. Rev. Tuberc., 70, 955, 1954. (92) Idem: Ibid., 70, 977, 1954. (93) **Hollander, A. G., Frobisher, M., Jr.,** and **Kalish, K.:** Ibid., 67, 497, 1953. (94) **Hosty, T. S., Freeman, B.,** and **Irwin, C.:** Pub. Health Lab., 11, 143, 1953. (95) **Howard, R. M., Brees, A.,** and **Henderson, M. G.:** Tr. Chemother. Tuberc., 351, 1952. (96) **Hoyt, A., Smith, C. R.,** and **Gribkoff, G. P.:** Am. Rev. Tuberc., 70, 916, 1954. (97) **Hsiung, G. D.,** and **Haley, L. D.:** Ibid., 70, 912, 1954.

(98) **Ilavsky, J.:** Proc. Soc. Exper. Biol. & Med., 84, 526, 1953.

(99) **Jorgensen, J. B.,** and **Ringstad, F.:** Acta Path. et Microbiol. Scand., 32, 465, 1953.

(100) **Kahn, M. C.:** Am. Rev. Tuberc., 20, 150, 1929. (101) **Karlson, A. G.:** Ibid., 70, 531, 1954. (102) **Karlson, A. G.,** and **Ikemi, Y.:** Proc. Staff Meetings, Mayo Clin., 27, 373, 1952. (103) Iidem: Ibid., 29, 119, 1954. (104) **Keogh, E. V., North, E. A.,** and **Warburton, M. F.:** Nature (Lond.), 161, 687, 1948. (105) **Kirby, W. M. M., Burnell, J. M.,** and **O'Leary, B.:** Am. Rev. Tuberc., 64, 71, 1951. (106) **Kirchner, O.:** Zentralbl. Bakt., I. Abt. Orig., 124, 403, 1932. (107) **Koch, R.:** Berlin klin. Wchnschr., 19, 221, 1882. (108) **Koenigstein, R. P., Cheng, P. S., Koenigstein, K.,** and **Suen, I. D.:** Wien. klin. Wchnschr., 63, 723, 1951. (109) **Konowalchuk, J.,** and **Reed, G. B.:** Canad. J. Med. Sci., 29, 263, 1951. (110) **Kotani, S., Tsujimoto, T., Takuchi, K.,** and **Seki, T.:** Med. J. Oska Univ., 4, 9, 1953. (111) **Krasnow, I., Wayne, L. G.,** and **Salkin, D.:** Am. Rev. Tuberc., 71, 361, 1955. (112) **Kroger, E.,** and **Bosse, W.:** Zentralbl. Bakt., I Abt. Orig., 161, 198, 1954. (113) **Kruml, J., Prerovsky, I., Trefny, Z.,** and **Zuffickova, J.:** Cas. Lék. Ces., 89, 841, 1950.

(114) **Langenscheidt, E.:** Zentralbl. Bakt., I. Abt. Orig., 160, 165, 1954. (115) **Lecocq, E., Dubois, R.,** and **Rinz, R.:** Ann. Inst. Pasteur, 87, 141, 1954. (116) **Lee, H. F.:** Ann. New York Acad. Sci., 52, 692, 1949. (117) **Lee, H. F.,** and **Stavitsky, A. B.:** Am. Rev. Tuberc., 55, 262, 1947. (118) **Lee, H. F., Stavitsky, A. B.,** and **Lee, M. P.:** Proc. Soc. Exper. Biol. & Med., 61, 143, 1946. (119) **Levine, M.:** Ibid., 76, 171, 1951. (120) **Lewin, E.,** and **Hirsch, J. G.:** Am. Rev. Tuberc., 71, 447, 1955. (121) **Lowry, H.,** and **Berry, J. W.:** Am. J. Clin. Path., 20, 273, 1950. (122) **Lucentini, L.,** and **Boisvert, H.:** Ann. Inst. Pasteur, 82, 55, 1952.

(123) **Maccabe, A. F.,** and **Gould, J. C.:** J. Clin. Path., 7, 45, 1954. (124) **Maher-Loughnan, G. P.,** and **Hilson, G. R. E.:** Tubercle (Lond.), 33, 297, 1952. (125) **Maillard, E. R.,** and **Gagliardo, F. J.:** Am. Rev. Tuberc., 64, 675, 1951. (126) **Mankiewicz, E.:** Canad. J. Microbiol., 1, 85, 1954. (127) Idem: Unpublished data, 1955. (128) **McDerman, S. C.:** Trans. Chemother. Tuberc., 173, 1951. (129) **McNelly, E.,** and **Riddell, W. A.:** Am. J. Pub. Health, 39, 1463, 1949. (130) **Melvin, I., Klein, G. C., Jones, W.,** and **Cummings, M. M.:** Am. Rev. Tuberc., 63, 459, 1951. (131) **Meynell, G. G.:** J. Path. Bact., 67, 137, 1954. (132) **Middlebrook, G.:** J. Clin.

Invest., **29,** 1480, 1950. (**133**) Idem: Am. Rev. Tuberc., **62,** 223, 1950. (**133a**) Idem: Ibid., **69,** 471, 1954. (**134**) **Middlebrook, G.,** and **Cohn, M. L.:** Science, **118,** 297, 1953. (**135**) **Middlebrook, G.,** and **Dubos, R. J.:** J. Exper. Med., **88,** 521, 1948. (**136**) **Middlebrook, G., Dubos, R. J.,** and **Pierce, C.:** Ibid., **86,** 175, 1947. (**137**) **Miller, R.:** Am. Rev. Tuberc., **70,** 1053, 1954. (**138**) **Mishulow, L.:** J. Infect. Dis., **51,** 416, 1932. (**139**) **Mollov, M.,** and **Kott, T. J.:** Am. Rev. Tuberc., **65,** 194, 1952. (**140**) **Moore, M.:** Am. J. Path., **18,** 827, 1942. (**141**) **Morgante, O.,** and **Murray, E. G. D.:** Canad. J. Microbiol., **1,** 331, 1955. (**142**) **Morse, W. C., Dail, M. C.,** and **Olitzky, I.:** Am. J. Pub. Health, **43,** 36, 1953. (**143**) **Muether, R. O.,** and **MacDonald, W. C.:** J. Lab. & Clin. Med., **30,** 411, 1945. (**144**) **Noll, H.,** and **Bloch, H.:** J. Biol. Chem., **214,** 251, 1955. (**145**) **Nommik, S.,** and **Meakins, J. F.:** Canad. Med. Assn. J., **69,** 140, 1953.

(**146**) **Oeding, P.:** Acta tuberc. Scandinav., **25,** 208, 1951. (**147**) **Orlando, N. D.,** and **Bolduan, O. E. A.:** Bact. Proc., 26, 1953.

(**148**) **Paraf, J.,** and **Desbordes, J.:** Bull. Soc. Méd. Hôp. Paris, **65,** 1355, 1949. (**149**) **Parran, T.:** Am. Rev. Tuberc., **50,** 365, 1944. (**150**) **Pätiälä, J.:** Acta tuberc. Scandinav., **22,** 227, 1948. (**151**) **Patnode, R. A.:** Am. J. Pub. Health, **45,** 451, 1955. (**152**) **Patnode, R. A., Wrinkle, C. K.,** and **Beasley, C.:** Am. Rev. Tuberc., **69,** 599, 1954. (**153**) **Peizer, L. R., Widelock, D.,** and **Klein, S.:** Ibid., **68,** 290, 1953. (**154**) **Petragnani, G.:** Boll. Ist. Sieroterap. Milan., **5,** 173, 1926. (**155**) **Petroff, S. A.:** Am. Rev. Tuberc., **3,** 683, 1920. (**156**) **Pinner, M.:** Ibid., **11,** 139, 1925. (**157**) Idem: Pulmonary Tuberculosis in the Adult. Springfield, Ill.: Charles C Thomas, 1955. (**158**) **Pierce, C., Dubos, R. J.,** and **Middlebrook, G.:** J. Exper. Med., **86,** 159, 1947. (**159**) **Pound, A. W.:** J. Path. Bact., **64,** 131, 1952. (**160**) **Pryce, E. M.:** Ibid., **53,** 327, 1941. (**161**) **Pugh, D. L., Jones, E. R.,** and **Martin, W. J.:** Lancet, **2,** 92, 1950.

(**162**) **Reed, R. W.:** Canad. J. Med. Sci., **31,** 367, 1953. (**163**) Idem: Canad. J. Microbiol., **1,** 30, 1954. (**164**) **Remisch, E.:** Am. J. Clin. Path., **23,** 929, 1953. (**165**) **Reisner, D.:** Am. Rev. Tuberc., **57,** 229, 1948. (**166**) **Rheins, M. S.,** and **Thurston, J. R.:** Ibid., **72,** 210, 1955. (**167**) **Rheins, M. S., Thurston, J. R.,** and **Newton, N.:** Am. J. Med. Technol., **20,** 254, 1954. (**168**) **Rice, H. M.,** and **Rowan, F. C.:** J. Clin. Path., **6,** 261, 1953. (**169**) **Richardson Jones, A.,** and **Hinson, K. F. W.:** Am. Rev. Tuberc., **68,** 739, 1953. (**170**) **Richmond, L.,** and **Cummings, M. M.:** Ibid., **62,** 632, 1950. (**171**) **Roberts, E. G., Wallace, J. L.,** and **Erlich, H.:** Ibid., **61,** 563, 1950. (**172**) **Rogers, D. E., Cooke, G. M.,** and **Meyers, C. E.:** Ibid., **71,** 371, 1955. (**173**) **Rosenberg, K. S.:** Lancet, **1,** 615, 1943. (**174**) **Rothbard, S., Dooneieff, A. S.,** and **Hite, K. E.:** Proc. Soc. Exper. Biol. & Med., **74,** 72, 1950. (**175**) **Rowe, C., Spain, D. M.,** and **Childress, W. G.:** Am. Rev. Tuberc., **66,** 621, 1952. (**176**) **Rubbo, S. D.,** and **Morris, D. M.:** J. Clin. Path., **4,** 173, 1951. (**177**) **Rubbo, S. D., Woodruff, P. S.,** and **Morris, D. M.:** Nature (Lond.), **164,** 313, 1949.

(**178**) **Schwabacher, H.:** Tubercle (Lond.), **18,** 199, 1936–37. (**179**) **Schwartz, B., Mandelbaum, T., Spitz, L. J., Schmidt, P. P.,** and **Battaglia, B.:** Am. Rev. Tuberc., **66,** 594, 1952. (**180**) **Scott, N. B., Smith, D. T.,** and **Durham, N. C.:** J. Lab. & Clin. Med., **35,** 303, 1950. (**181**) **Shaffer, M. F.:** Am. Rev. Tuberc., **27,** 259, 1933. (**182**) **Sievers, O.:** Lancet, **1,** 798, 1949. (**183**) **Simpson, D. M.,** and **Reed, R. W.:** Canad. J. Microbiol., **1,** 495, 1955. (**184**) Iidem: Canad. J. Pub. Health, **1,** 43, 1956. (**185**) Iidem: Unpublished data, 1955. (**186**) **Smith, C. R.:** Am. J. Clin. Path., **21,** 274, 1951. (**187**) Idem: Am. Rev. Tuberc., **63,** 470, 1951. (**188**) **Smith, D. T.,** and **Scott, N. B.:** Ibid., **62,** 121, 1950. (**189**) **Sohier, R.:** Bull. Méd. (Paris), **63,** 461, 1949. (**190**) **Sohier, R., Juillard, J.,** and **Trimberger, J.:** Ann. Inst. Pasteur, **78,** 283, 1950. (**191**) **Srna, G.,** and **Hackel, H.:** Wien. med. Wchnschr., **103,** 326, 1953. (**192**) **Steenken, W., Jr.,** and **Wolinsky, E.:** Am. Rev. Tuberc., **68,** 548, 1953. (**193**) **Sula, L.:** Pub. Health Rep., **63,** 867, 1948. (194) **Suter, W. E.,** and **Dubos, R. J.:** J. Exper. Med., **93,** 559, 1951.

(**195**) **Tarshis, M. S.:** J. Lab. & Clin. Med., **40,** 3, 1952. (**196**) Idem: Am. J. Clin. Path., **23,** 661, 1953. (**197**) Idem: J. Bact., **67,** 117, 1954. (**198**) **Tarshis, M. S.,** and **Frisch, A. W.:** Am. J. Clin. Path., **21,** 101, 1951. (**199**) Iidem: Ibid., **21,** 729, 1951. (**200**) **Tarshis, M. S., Kinsella, P. C.,** and **Parker, M. V.:** J. Bact., **66,** 448, 1953. (**201**) **Tarshis, M. S., Parker, M. V.,** and **Dunham, W. B.:** Acta tuberc. Scandinav.,

**30,** 37, 1954. (**202**) Iidem: Ibid., **31,** 92, 1955. (**203**) **Tarshis, M. S., Weed, L. A., Kinsella, P. C., Parker, M. V.,** and **Dunham, W. B.:** Am. J. Pub. Health, **45,** 1157, 1955. (**204**) **Thalhimer, W.,** and **Rowe, C.:** Am. Rev. Tuberc., **63,** 667, 1951. (**205**) **Tsuneishi, N.,** and **Goetz, A.:** Bact. Proc., 108, 1955.

(206) **Vaccaro, H.,** and **Alonso, G.:** Rev. Méd. Chile, **79,** 31, 1951. (**207**) **Vaccaro, H., Alonso, G.,** and **Mordoh, I.:** Ibid., **79,** 110, 1951.

(208) **Wayne, L. G.:** Bact. Proc., 92, 1954. (**209**) Idem: Ibid., 108, 1955. (**210**) Idem: J. Bact., **69,** 92, 1955. (**211**) **Weed, L. A.:** Am. J. Clin. Path., **21,** 673, 1951. (**212**) Idem: Ibid., **21,** 691, 1951. (**213**) **Weir, J. M.:** Proc. Soc. Exper. Biol. & Med., **46,** 47, 1941. (**214**) **Whalen, J. W.,** and **Mallmann, W. L.:** Am. Rev. Tuberc., **71,** 382, 1955. (**215**) **Wherry, W. B.,** and **Ervin, D. M.:** J. Infect. Dis., **22,** 194, 1918. (**215a**) **Wilson, F. J., Kalish, C.,** and **Fish, C. H.:** Am. Rev. Tuberc., **65,** 187, 1952. (**216**) **Wright, A. E.:** Lancet, **1,** 218, 1924. (**217**) **Wrinkle, C. K.,** and **Patnode, R. A.:** Am. Rev. Tuberc., **66,** 99, 1952.

(218) **Yamamoto, H.:** Acta tuberc. Japon., **2,** 78, 1952. (**219**) **Yegian, D.,** and **Kurung, J.:** Am. Rev. Tuberc., **65,** 181, 1952. (**220**) **Young, R. M.,** and **Leonard, W. A.:** Am. J. Clin. Path., **21,** 1045, 1951. (**221**) **Yukischige, K.:** Jap. J. Bact., **9,** 857, 1954. (**222**) Idem: Ibid., **9,** 935, 1954.

## SUMMARIO IN INTERLINGUA

*(See page 313 for original article)*

### Le Relation Inter Apparentia e Comportamento del Insulas de Langerhans in Humanos

Specimens bioptic del pancreas de 3 diabeticos es examinate in le lumine del subsequente curso del morbo. Post ablation de un pheochromocytoma, un patiente recuperava ab su diabete. Le condition de un secunde patiente se meliorava sed ille non recuperava. (Recuperation se defini hic como retorno del test de tolerantia de glucosa a limites normal.) Un tertie patiente esseva meliorate sed continuava requirer insulina post adrenalectomia total pro syndrome de Cushing. Iste observationes preliminari in humanos es comparate con observationes de diabete experimental con le objectivo de relationar le morphologia del insulas de Langerhans con lor capacitate functional sub varie conditiones.

## PREVENTIVE MEDICINE AND EPIDEMIOLOGY

UNDER THE CHARGE OF

JOHN E. GORDON, M.D.

PROFESSOR OF PREVENTIVE MEDICINE AND EPIDEMIOLOGY
HARVARD UNIVERSITY SCHOOL OF PUBLIC HEALTH

AND

THEODORE H. INGALLS, M.D.

ASSOCIATE PROFESSOR OF EPIDEMIOLOGY
HARVARD UNIVERSITY SCHOOL OF PUBLIC HEALTH
BOSTON, MASSACHUSETTS

# ARCTIC ENVIRONMENT AND INTESTINAL INFECTION

BY JOAN G. BABBOTT, M.D.

FRANK L. BABBOTT, JR., M.D.

AND

JOHN E. GORDON, M.D.

(From the Department of Epidemiology, Harvard University School of Public Health, Boston, Massachusetts. This study was supported in part by the Commission on Environmental Hygiene, Armed Forces Epidemiological Board, and Office of The Surgeon General, Department of the Army, Washington, D. C.)

INCREASINGLY the Arctic draws the attention of this modern world, and for diverse reasons. The natural resources of the Far North are an evident attraction as demand grows for more fuel to feed the furnaces of twentieth century industry. Population pressures increase almost everywhere[35] and seek an outlet even in the harsh environment of Arctic and Subarctic. The air age finds international transport and traffic directed to advantage over a polar route. Political conflict and the ambition of nations raise considerations of military strategy which center at the top of the world. All of these affairs have a relation to health.

*Natural Resources.* The Arctic has many raw materials and their production has increased rapidly. The Alaska salmon industry[81b], for example, grossed $81,000,000 in 1949, and 60,000,000 boardfeet of cut timber came from Alaskan mills which had tripled in number between 1940 and 1950. The mining communities of Gällivare and Kiruna above the Arctic Circle in Sweden ship out close to 12,000,000 tons of high grade iron ore[25] annually in operations which proceed around the clock. Information from Soviet Russia is less recent and harder to come by, but the world's largest apatite deposits[85a] are near Kirovsk and even by 1938 were producing 2,000,000 tons annually. Similarly about a third of all lumber cut in the Soviet Union comes from the northern European section of that country. Although not as impressive in world markets, the economy of Greenland[69] has shown a steady increase. Cryolite mining is the largest industry, producing 46,000 tons annually in recent years; and sheep rais-

ing, begun with 700 animals in 1915, had grown to 19,000 in 1953.

The Arctic is an expanding area economically. The health of workers in polar regions is no less a consideration than in the industrialized cities to the south. The natural resources of the region are a compelling influence on central government and it so happens that every part of the Arctic is a political unit of a populous country with its capital in a temperate climate and capable of providing good health service and medical care. The situation thereby differs from most underdeveloped areas of the tropics where aid is at the discretion of a friendly neighbor or of a governing colonial power, both irregularly motivated by benevolence and self-interest.

TABLE 1.—POPULATION, TERRITORY OF ALASKA, BY CENSUS YEARS, 1920–1950

| *Year* | *Population* |
|---|---|
| 1920 | 54,441 |
| 1930 | 59,278 |
| 1940 | 72,524 |
| 1950 | 128,643 |

Source: U.S. Census, Bureau of the Census, 1920–1950.

*Population Growth.* The number of people living within the Arctic Circle and in the adjoining Subarctic has increased in proportion to the growing economy. The trend in Alaska is shown in Table 1; the population has more than doubled in 30 years. Estimates for 1953 give a population of 205,000, this including troops stationed in the Territory as well as established residents.

A loose estimate of population increase in Soviet Russia, north of 60° N. latitude, is as follows: 1926: 1,869,095; 1939: 3,814,200; 1947: 4,210,000. The city of Murmansk[85a] alone grew from 8,777 inhabitants in 1926 to about 160,000 in 1940.

Even Greenland[69] has doubled its population during the last 50 years, to a level of 23,360 people in 1952.

Most of the gains in population are through immigration. The Lapps and Eskimos are no newcomers and indeed they have done well to hold their numbers. Populations of the Arctic now are predominantly of ethnic groups whose permanent penetration is measured in little more than decades. These settlers are mainly from other parts of the same country. They move north with established ideas of the nature and value of good health services, and as a consequence are a strong force toward improved conditions in their new environment.

*Military Considerations.* The strategic importance of polar areas has received much emphasis[54,81b]. Only 60 miles separate the Chukchi Peninsula west of the Bering Strait from the Alaskan Seward Peninsula to the east. The shortest distance between industrial centers of the United States and Soviet Russia lies across the ice floes of the Polar Sea. General William Mitchell[69], in pleading the cause of air power, long ago said he who holds Alaska holds the world! Irrespective of how true that is, the Arctic is clearly the geographic frontier of the United States. The strategic and tactical influence of disease[33a] is presumably as important in arctic military operations as it has been in other theaters of war.

*Transport and Trade.* Scheduled commercial air routes from Europe to California now pass within 900 miles of the North Pole. Plans this year are for still further penetration of the Arctic, with flights from Scandinavia to Tokyo by way of Fairbanks and Anchorage. At least two great nations have regular weather and reconnaissance flights over the top of the world. These operations demand the same careful assay of health conditions and health hazards

that made flying in the tropics safe for passengers, crew and the ground staff of air bases.

**Concept of an Arctic Epidemiology.** The justification for an enlarged concern about health and disease in arctic areas will rest on the four considerations just presented. There are others.

The foundation for improved health services and a scheme for medical care is to be had from principles established by experience elsewhere. A definition of the particular problems of the Arctic presumably will come from the same source that led to recognition of those principles: the field study of disease in nature, the epidemiologic method. As diagnosis precedes treatment in clinical medicine, so epidemiologic analysis is the guide to public health practice[33c].

An arctic epidemiology requires recognition of two soundly pertinent principles. The first has to do with the physical nature of these polar and subpolar regions. All are not to be taken as a unit. Impressive differences exist in physical environment, differences scarcely to be appreciated without experiencing them. If the conventional view of the tropics is that of a steaming jungle, the popular view of the Arctic is likely a bleak shore with an Eskimo in the foreground and an iceberg floating in the rear. Both situations exist, but only in part. What is necessary to remember is that conspicuous differences in climate and environment occur within the same latitude. Just as the tropics have the hot, wet rainforest, the hot dry grasslands, the desert and the monsoons, so the Arctic has its tundra, taiga and permafrost, its mountains, and its coastal areas in some instances so modified by ocean currents as to give the curious situation where the warmer part of Norway is to the north and the cooler part to the south. These environmental differences are reflected in the populations that live there, in respect to size, density, occupation, social customs and habit, and thus in the diseases they have.

The second principle derives from the first. If the aim is to determine the modification of disease under the influence of cold climate, disease entities are necessarily observed under a variety of existing conditions, in distinctive areas, and disease by disease. The pattern of study is provided by the tropics[34] and outstanding examples rest in the accrued knowledge of malaria[57] and yellow fever[79].

The start of observations toward an arctic epidemiology is with the medical history of a region, the purpose being to learn the general characteristics of disease behavior, the problems of particular weight, and those seemingly more or less peculiar to the area.

Interest turns next to recorded information about a selected disease or group of diseases. The vital statistics of the area, reported cases and deaths, are compared with neighboring regions and with usual behavior in well studied situations. The data are examined for variations over periods of time, and critically for reliability and completeness. A second and commonly the more productive source of information is in special studies of other workers, on the particular condition itself and on allied problems. The basic consideration of time-place-person relationships is defined.

In search for causes of behavior and origin of mass disease, the collected information is next arranged within the matrix of a model permitting ecologic analysis. That which gives emphasis to an agent of disease, to a host population attacked, and to an environment acting on both has proved satisfactory under a variety of circumstances[33b]. The structure built around the framework of the model is enlarged by fun-

damental and general information pertaining to these three elements. The central objective is to identify gaps in knowledge inhibiting practical understanding of the disease, and hence prevention and control. Direction is given to subsequent investigations to meet a defined need. These invariably lead to field study in nature. Some facts are only to be had by that method. Others better suited to systematic search in clinic or laboratory require eventual field test for practicability and application. The principle of field study is recognized in every arctic country. American activity has given rise to the Arctic Health Research Center of the Public Health Service in Anchorage; and to the Arctic Aeromedical Laboratory of the Air Force, with a base at Fairbanks.

Practical effort toward defining epidemiological attributes of the Arctic has a choice of a number of regions and a variety of disease processes. Our personal interests have centered on the acute communicable diseases of the intestinal tract. That choice was because the basic epidemiologic facts about this group of diseases are better known than for any other. Since laboratory methods are an integral part of modern field procedure, the relative simplicity of technical method for intestinal pathogens is well suited to the rigorous conditions under which the work has to be done. The state of environmental sanitation in most parts of the Arctic gives this group of infections high rank among health problems.

Our experience includes an acquaintance with Alaska, Labrador and the northern districts of Norway, Sweden and Finland. Field operations have been conducted in Alaska, are underway in Finland and are projected for Greenland. The present purpose is to bring together something of the environmental conditions which govern disease behavior in cold climates, to recount available facts on intestinal infections in the Arctic, and to give the background of field studies on modes of transmission designed to determine the relative part of contact and vehicle in the spread of intestinal pathogens under distinctive conditions of the northern environment.

TABLE 2.—LEADING CAUSES OF DEATH, ALASKA AND CONTINENTAL U. S. A., DEATHS PER 100,000 POPULATION, 1953

| *Cause of Death* | *Alaska* | *Continental United States* |
|---|---|---|
| Accidents | 122.9 | 60.8 |
| Heart Disease | 122.4 | 357.6 |
| Congenital Malformations and Diseases of Early Infancy | 77.1 | 53.2 |
| Tuberculosis | 60.5 | 12.5 |
| Influenza and Pneumonia | 39.5 | 33.0 |
| Cancer | 37.1 | 144.7 |
| Ill-defined Causes | 29.8 | 12.7 |
| Cerebral Hemorrhage | 27.8 | 108.2 |
| All Other Causes | 118.5 | 176.2 |
| All Causes | 635.6 | 958.9 |

Source: Alaska Department of Health

TABLE 3.—CAUSES OF DEATH IN WEST AND NORTH GREENLAND, 1952

| *Cause of Death* | *Per cent Total Deaths* |
|---|---|
| Tuberculosis, all forms | 39.2 |
| Pneumonia and influenza | 15.2 |
| Diseases of early infancy | 8.3 |
| Accidents and trauma | 7.6 |
| Heart disease | 6.7 |
| Cancer | 2.5 |
| Meningitis | 2.2 |
| Cerebral vascular disease | 1.6 |
| Indefinite and all other causes | 16.7 |

Source: Report on Greenland, 1954
The Prime Minister's Second Department
The Greenland Department
Copenhagen, Denmark, 1954.

**Comparison of Disease Behavior in Arctic and Temperate Climates.** The Arctic has no unique illnesses[77] although the relative importance of certain disease processes does stand in relation to northern geographic location. Table 2 compares the ten leading causes of death in Alaska with those of con-

tinental United States for the year 1953. The distribution of total deaths in Greenland[66] for the year 1952 is given in Table 3. Two things are striking.

The first is the relatively high standing of the infectious diseases, particularly tuberculosis, in these northern countries. Recent preliminary figures from Alaska show, however, that tuberculosis has dropped to third place as a cause of death[2a]; and Greenland, in the midst of a comprehensive campaign to bring this disease under control, has reduced the lead in morbidity and mortality[5].

A second main observation from the Alaskan data is that accidents are the single most common cause of death, taking the Territory as a whole. This is unusual and yet not wholly surprising, for the population is weighted by young adult males employed in the hazardous occupations of construction, mining, lumbering and fisheries. In this setting the significance of alcoholism and suicide also is more or less expected, as is the lesser importance of cardiovascular disease and cancer.

The incidence of tuberculosis is so great among Eskimos that it may well be considered the main epidemic disease of the north. Since first contact with the white man, the disease has caused more deaths than any other. Few native households in Alaska today fail to have some member either under treatment or convalescent. A high incidence of tuberculosis is also characteristic of Greenland, Labrador, and to a considerable extent in the Lapp population of Scandinavia[4].

Great epidemics have been frequent among peoples of the north. The first recorded outbreak of smallpox in Alaska occurred in 1836 while the Territory was under Russian control. Close to 60% of the native population is believed to have died and entire villages were wiped out[3,49]. The Klondike gold rush of 1897 brought an influx of prospectors and epidemics of typhoid fever, pneumonia and meningitis.

Measles is of both historical and contemporary interest. Epidemics of fifty years ago carried fatality rates in Alaska of 25% to 75% among Eskimos and Indians. Villages in the Kuskokwim region[77] were decimated by this disease along with what appears to have been pneumonia. A recent outbreak[51] gave an attack rate of 96% in an isolated Indian settlement of 135 people. With one exception, the only persons spared were older than 70 years. A classic epidemic ranking with that of the Faroe Islands[58] occurred in southern Greenland[15] in 1951. The population had no previous history of measles. Infection was introduced by a recent arrival from Denmark. He attended a community dance while in the prodromal stage of measles. Within 40 days, 4,221 of the 4,320 inhabitants of the Julianehaab District came down with the disease. All age groups were involved and there were 77 deaths.

The "stranger's cold" is a common phenomenon. The visit of the first ship to Spitzbergen[59] every spring touches off a round of upper respiratory infections in a previously healthy population. Among Eskimos[77] the seasons of greatest mobility bring increased contact and coincide with an annual frequency of respiratory infection. Influenza has been a notorious cause of death in the north. Its effect is both direct and secondary, for among coastal Eskimos the availability of sea mammals may be restricted to a few days a year. A village incapacitated at this time faces subsequent starvation[69,72].

As for nutritional deficiency diseases, scurvy has always held an important place in the Arctic, particularly among Europeans. Bering, the Danish sea captain who led Russian expeditions in search of the Northwest Passage and

was the first known white man to visit Alaska[3], himself died of scurvy on his second voyage in 1741. A hundred years later[77] an entire party of 129 men led by Sir John Franklin died of scurvy and starvation.

**Some Demographic Aspects of the Arctic.** Vital statistics on births, deaths, marriages and matters of health are to be regarded for most arctic regions with much skepticism. Since a population stands in the same relation to the epidemiologist as does the individual patient to the clinician, these data require examination if an understanding is to be had of health and disease in the larger unit of observation. They provide the means by which to determine the structure and function of a population. Consequently the known facts about arctic populations are brought together, and evaluated in respect to limitations and deficiencies. The first consideration is of numbers of people.

The Soviet Union is easily the largest political entity having territory within the Arctic. As of 1947, estimates are of some 4,210,000 people living in European Russia and Siberia[85a] above 60° N. latitude. The Scandinavian Arctic comes next with about 745,000 by recent enumeration. This includes 250,000 in Swedish Norbotten[24], 400,000 in the three northern Norwegian districts of Finnmark, Troms and Nordland[80] and 95,000 in Finnish Lapland[56].

The population of Alaska[66] in 1950 was 128,643. The Canadian census of 1951[93] shows a combined population for Labrador, Northwest Territory and Yukon Territory of about 31,000. Persons living in the northern reaches of British Columbia, Alberta, Saskatchewan, Manitoba, Ontario and Quebec are reasonably to be included, to give a total arctic and subarctic population of about 50,000 people. Greenland[66], a major arctic land area and an integral political division of Denmark, had a population of 24,118 at the beginning of 1952. Most of the data are not current and others represent little more than approximations.

By liberal estimate, about 5,250,000 people occupy a major part of land surface. Except for absolute desert and the Antarctic, population density in the Arctic is less than in any principal region of the world. In Alaska, as of 1950, only six communities could claim more than 2,500 people, and average density[3] was 0.2 person per square mile.

An attempt to separate arctic populations by ethnic or racial divisions is hazardous, because the risks of an arbitrary classification are added to the difficulties of enumerating scattered peoples. Some understanding is nevertheless requisite to public health practice, in order to assign priorities and initiate programs where most needed. The native minorities are the main consideration.

For several centuries some 20 ethnic groups[85a] have been recognized on the basis of language in the north Soviet Union. Fine distinction is difficult, for over the years some units lose their identity through merging with others. In estimating indigenous populations in 1945, Lappo[46] sometimes had to draw on 1926 census data, for the 1937 census had been suppressed and that of 1939 did not include several divisions known to exist. The total minority population was judged to be about 356,000 people, with the remainder of the 4,210,000 population of the Soviet Far North presumably of European extraction.

The Lapps, a resourceful and colorful people, are a small minority in northern Scandinavia. Their numbers approach 31,000 among an area population[17] of 745,000.

Racial mixing in Greenland has been so extensive over many years[15] that

all permanent residents are now called Greenlanders[70], with no attempt to distinguish Eskimo, part Eskimo and European. That is sensible and feasible in Greenland, for the peoples and their needs are much the same throughout the country.

A recent survey[3] illustrates the necessity in Alaska for separate appraisal of health problems of white and non-white peoples. Table 4 compares Numbers of each in 1920 and in 1950 are in Table 5. Total native population as of 1953 is estimated at 39,300.

Aside from numbers and comparative health status, geographic distribution of ethnic groups has much usefulness. In Alaska the white population is concentrated almost exclusively in the southeast panhandle and around Anchorage and Fairbanks. The approximately 40,000 non-whites are spread

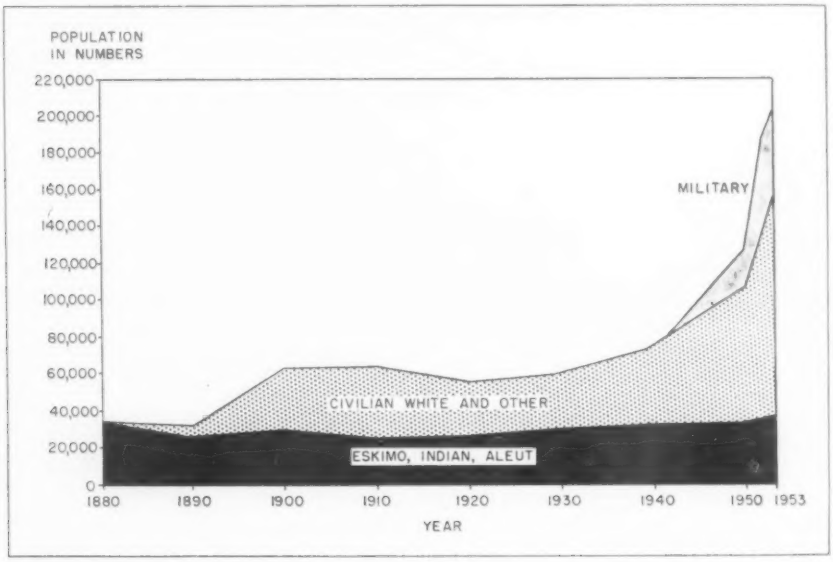


Fig. 1.—Population of Alaska, 1880–1953, Eskimo, Indian and Aleut; Civilian White and Other; and Military.

*Source:* Alaska Health Survey Team: Alaska's Health, A Survey Report, Graduate School of Public Health, University of Pittsburgh, 1954.

death rates by selected causes for the two groups. Interracial mingling has not been so extensive as in some other regions, although a half of Eskimos[71] are judged to have some Caucasian blood. The recent population increase[3] has been almost wholly in the white component (Fig. 1). Data for whites are probably more reliable but the apparent population stability of Eskimos, Indians and Aleuts is noteworthy.

across 500,000 square miles of territory; they live mainly in villages of less than 100 people, and the communities are often separated by 100 miles or more.

Demographic studies[3] reveal finally that an average of 5 to 6 persons inhabit a dwelling, which more often than not consists of one room. Thus Alaska, and indeed most northern countries, presents the anachronism of severe

overcrowding in a land of low population density as expressed by persons per square mile. The medical and public health implications are obvious.

The spread of most communicable diseases once introduced into a village is enhanced by overcrowding, close contact, and low levels of sanitation[3,37,77]. On the other hand, distances and difficulties in travel tend to protect communities from frequent exposure. A population of susceptibles is built up. As a consequence, when even the ordinary communicable diseases of childhood strike a community, they are a major source of morbidity, and the mortality is beyond usual limits.

Recent years have seen material progress in most parts of the Arctic toward a more comprehensive health service and an improved medical care despite the natural obstacles of distance, transport and small units of population. By necessity, the direction of effort has rested largely on estimates, assumptions, and analogy with what has proved successful under other conditions. What is needed now is a better knowledge of population characteristics, and of the behavior of disease as modified by climate. Routine report of cases and deaths can not be depended upon to supply this information. The answers seemingly are to be had only through field study, always arduous and in this instance especially so.

TABLE 4.—DEATHS PER 100,000 FROM SELECTED CAUSES, ALASKA, WHITE AND NATIVE POPULATIONS, 1953

| *Cause of Death* | *White Population* | *Native Population* |
|---|---|---|
| Heart Disease | 137.0 | 61.1 |
| Accidents | 108.6 | 183.2 |
| Congenital Malformations and Diseases of Early Infancy | 59.2 | 152.7 |
| Cancer | 35.0 | 45.8 |
| Cerebral Hemorrhage | 22.9 | 48.8 |
| Ill-defined Causes | 10.3 | 111.9 |
| Influenza and Pneumonia | 7.2 | 175.6 |
| Tuberculosis | 3.6 | 300.3 |
| All Others | 86.9 | 251.9 |
| All Causes | 470.7 | 1330.8 |

Source: Alaska Department of Health

**Physical Environment of the Arctic.** Arctic is a word of Greek origin having reference to the constellation of the Great Bear or Big Dipper, two stars of which point to the North Star. The North Star is itself so situated in relation to the axis of the earth that it assumes a virtually constant position above the North Pole[13,69,86]; in fact the brightness of this star and its apparent proximity is one of the features of the north country, along with the magnificent Northern Lights.

The imaginary line of the Arctic Circle ordinarily placed at parallel 66° 31′ N. latitude[64], derives from this astral concept of the Arctic. The Arctic Circle marks the southern boundary of territory where at least one day each summer the sun never dips below the horizon, and one day each winter it never

TABLE 5.—POPULATION COMPONENTS WHITE AND NATIVE, ALASKA 1920 AND 1950

| *Component* | *1920* | *1950* |
|---|---|---|
| White | 27,883 | 92,808 |
| Eskimo | 13,698 | 15,882 |
| Indian | 9,918 | 14,089 |
| Aleut | 2,942 | 3,892 |

Source: U.S. Census, Bureau of the Census, 1950.

appears. The number of such days is of course greater in progression northwards. A definition[64,73] of the Arctic as the region lying within the Arctic Circle is thus in terms of light and darkness, Fig. 2.

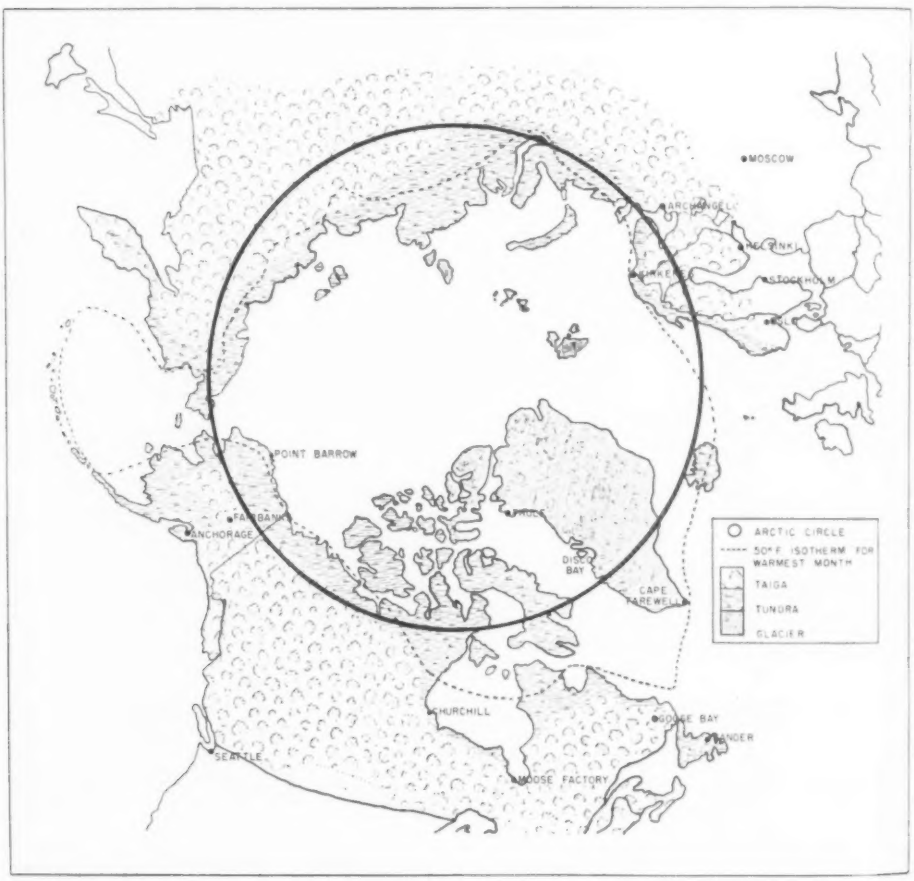


Fig. 2.—The Arctic and Subarctic—Tundra, Taiga, Glacier.

Climatologists limit the Arctic by temperature[13,73], sometimes to that area lying north of a boundary fixed by the +10° C. (50° F.) isotherm for the warmest month; or the isotherm −10° C. (14° F.) for the coldest month; or again those areas with a mean annual temperature of 0° C. (32° F.) or less. Isotherm[86] refers to a line joining points on the earth's surface having the same temperature at a given time, or the same mean temperature for a given period. The +10° C. isotherm falls north of the Arctic Circle for nearly all of the Eurasian and North American continents except in eastern Canada.

Botanical limits of the Arctic, another means of definition, are closely related to temperature; in fact, some botanists use the +10° C. isotherm as the boundary. Others prefer a biologic reference and reserve the term Arctic for that

region lying north of a line 80 kilometers (50 miles) beyond the limit of coniferous forests[13,61,73].

Agronomists define the Arctic as a northern region having fewer than 50 days between spring and fall frosts.

Politically within the Arctic lie greater or lesser portions of continental Soviet Russia, the United States, Canada, Norway, Sweden and Finland, the Greenland island province of Denmark, along with innumerable lesser islands and archipelagos and the vast Arctic Ocean.

Shelesnyak[73], in summarizing what is meant by Arctic, states "the fact remains that there is no one single definition capable of describing or delimiting this large and varied area, nor could it be so." In general, when used as a noun in this discussion, Arctic will refer to a geographical region within the Arctic Circle. When used as an adjective, it will have the climatic connotation.

*Arctic and Subarctic Terrain.* The Arctic Ocean with its perpetually ice-clogged heart, the Polar Sea, is the largest and most uniform element within the Arctic Circle. This body of water and ice, 2000 miles across, is in continuous motion. Tides are insignificant, but wind and currents account for the generally eastward Arctic Drift[55] which piles wood from Siberia on the shores of Franz Joseph Land, Spitzbergen, and Greenland. Recent Russian and American expeditions have set up semipermanent camps on large ice islands which move at a rate of a mile to a mile and a half a day along an erratic course, from an apparent origin off the coast of Canada out into the Polar Sea[60,85b] and thence east toward Greenland. Some ice islands up to twenty miles in length have been observed over a period of several years.

The Polar Basin has interest scientifically mainly in relation to oceanography, meteorology, terrestrial magnetism, and a study of ice. Permanent human habitation exists only on its periphery, and in small numbers. For military reasons and because of increasing sea and air traffic, understanding of this environment becomes as essential as others better suited to human life.

Tundra is commonly considered the typical terrain of arctic regions. A look at a world map showing natural vegetation supports this impression[64]. The borders of the Polar Basin are tundra. This may be only a few miles wide, as along the Greenland coast[63] and parts of north central Siberia, or may extend inland for hundreds of miles as northwest of Hudson Bay. It comprises a twentieth[10] of the surface of the earth.

Tundra is a Russian word of Lappic origin and refers[86] to the level or undulating treeless plains which mark the limit of arborescent vegetation. The tundra varies, being sometimes lightly wooded to include ground birch, dwarf willow, and heather; or grasses may predominate; or with little more than mosses and lichens.

Tundra regions are essentially arid in terms of annual precipitation, Fig. 3, but since the frozen subsoil prevents drainage, the result is a land of innumerable lakes and bogs. Grazing of reindeer, hunting, trapping, and fishing are the principal economy, although rich mineral deposits and potential oil reserves are known to exist. Many thousands of people live in tundra regions. The permafrost is a dominant environmental influence, in large measure determining mode of life and kind of disease.

To the south of the tundra is a second broad band of territory, the taiga, characteristic of both Arctic and Subarctic and marked by a particular vegetation. It has been described[86] as a vast, swampy, coniferous forest. Much of

eastern Siberian taiga has needleleaf deciduous trees; that of North America is predominantly evergreen. The geographic limits of taiga are broader than of tundra. On the North American continent taiga dips into the United States along the northwest shores of Lake Superior; it extends in a northwesterly direction to part of Hudson Bay, and at the mouth of the Mackenzie River almost to the Arctic Ocean. The Siberian boundaries have still greater spread. Within the taiga live millions of people, many subsisting on the primitive economies of hunting and fishing, and others engaged in most productive timber and mining operations. Much of the taiga is underlaid by permafrost and subject to the problems that situation brings.

Glacier covered land, as in Greenland, is a fourth type of arctic terrain; indeed this is the main component of the Antarctic where neither tundra nor taiga exist. The icecap which covers 86% of Greenland is a great flat dome[55, 63] having a base of some 700,000 square miles and a fairly constant elevation of between 8000 and 9500 feet. So uniform is the surface that Stefansson[77] states: "Excepting the snowfree coastal districts and the crevassed regions where the ice flows down toward the

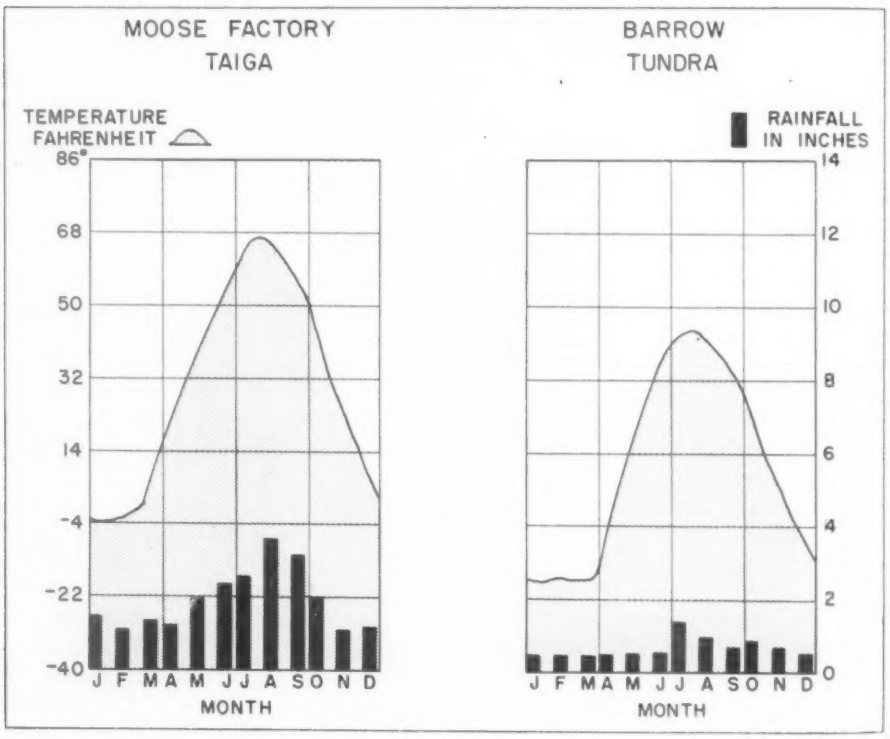


Fig. 3.—Temperature (Degrees Fahrenheit) and Rainfall (Inches) for Taiga (Moose Factory, Canada) and Tundra (Barrow, Alaska).
*Source:* Trewartha, G. T.: An Introduction to Weather and Climate, New York, McGraw-Hill, 1943.

sea, Greenland is practically one continuous and nearly perfect landing field for a plane equipped with skis." The glacial portion of Greenland is of little concern to medicine and public health because inhabitants are concentrated along the coast, which is mainly tundra. As with the Polar Basin, however, problems of survival in glacial areas are being studied.

*Temperature in Arctic Regions.* If the Arctic has any single connotation in the mind of the uninitiated it is that of bitter cold. The Arctic is cold, but in places no colder than many north temperate latitudes; it has seasonal variations which may be extreme. As a matter of fact, there is nothing static about climate in the Arctic or anywhere else[52], if by climate is meant average measures of temperature, humidity, and precipitation taken over years or decades.

For thousands of years the world has been moving out of the Ice Age, but this gradual warming process is not without fluctuations. Dunbar[19] mentions two periods of warming in arctic areas, one in 1870–1880, affecting particularly the Canadian eastern Arctic; and a second and more recent between 1915 and 1945, with an obvious influence on Spitzbergen and West Greenland. Along the latter coast the warmer waters sharply decreased the catch of sea mammals, and at the same time led to appearance of enormous numbers of Atlantic cod. The result was a significant change in the economy of West Greenlanders[27,45b,48], where self-sufficient individual hunters were replaced by a centralized and co-operative society having money as its base.

The damping effect of the ocean on land temperatures is well established. Off Norway the benevolent Gulf Stream maintains open water throughout the year, all the way to Kirkenes[17] some 250 miles above the Arctic Circle. Summers along this coast are cool and snowfall is minimal in winter. Similarly, the cold Labrador Current prevents extremes in summer temperature along that coast.

Inland or continental arctic climates[55] ordinarily are characterized by greater temperature variation and less precipitation than coastal regions. The record maximum given by Stefansson for readings within the Arctic Circle was +100° F. at Fort Yukon, Alaska, although temperatures in the range of +95° F. are frequent in many localities. Again according to Stefansson, Verkhoyansk in the Siberian Arctic holds the record official low of −94° F., although unofficial readings in Oimekon, Siberia[77], 200 miles south of the Arctic Circle, suggest that this may some day have the dubious honor of being the coldest place on earth. Table 6 gives temperature means and extremes, and annual precipitation for selected communities in the Alaskan Arctic and Subarctic.

*Permafrost.* This refers to ground, regardless of its composition and water content, having temperatures never higher than freezing at any point in annual fluctuations[11,53]. The frozen state sometimes has existed for thousands of years and may penetrate many hundreds of feet. Permafrost is covered to varying depths by an active layer of soil which goes through seasonal cycles of freezing and thawing, and provides plants with nutrients.

About a fifth of the world is underlaid by permafrost. The distribution is spotty, bearing little relation to any isotherm and none to the Arctic Circle. For example, only small isolated areas of permanently frozen ground exist in Scandinavia. By contrast, almost all of Siberia falls within the boundaries of permafrost, close to 80% of Alaska, and a half of Canada.

The presence of permafrost relates strongly to problems of sanitary engi-

neering in the Arctic, to food supply and to the habits and customs of the people, matters to be presented in connection with biologic and social environment. Water supply is among the important considerations.

*Water Supply.* Water is a precious commodity in many arctic areas, to be used sparingly, in this respect rivalling large parts of the tropics and this despite being so much a land of snow and ice. Residents of temperate zones come to take water supply more or less for granted, with little appreciation that have no outlet, and lose water solely by evaporation. Such sources, once polluted, remain so for long periods because cold inhibits biologic oxidation of organic material and permafrost eliminates the purifying action of filtration[67].

*Effect of Physical Environment on the Human Host.* Man is essentially a tropical animal, and much attention has been given his adaptation to an alien arctic environment. It is worthwhile to emphasize that while man can live effectively[69] at temperatures as low

TABLE 6.—CLIMATE IN ALASKA

| | | Temperature | | | | | |
|---|---|---|---|---|---|---|---|
| *District* | *Station* | *January Average* (° *F.*) | *July Average* (° *F.*) | *Max.* (° *F.*) | *Min.* (° *F.*) | *Growing Season* (*Days*) | *Annual Precipitation* (*Inches*) |
| Southeastern | Ketchikan | 32.6 | 51.5 | 96 | —8 | 165 | 150.89 |
| Pacific Coast | Seward | 22.4 | 55.3 | 82 | —20 | 132 | 78.78 |
| Southwestern | Dutch Harbor | 32.2 | 51.3 | 80 | 8 | 145 | 56.77 |
| Southern Valley | Anchorage | 11.2 | 57.0 | 92 | —36 | 110 | 14.32 |
| | Bethel | 8.3 | 54.5 | 90 | —46 | 93 | 17.98 |
| Bering Sea | Nome | 3.4 | 49.8 | 84 | —47 | 52 | 17.82 |
| Yukon Valley | Fairbanks | —11.6 | 60.0 | 99 | —66 | 89 | 11.87 |
| Arctic drainage | Barrow | —17.0 | 40.2 | 78 | —56 | 23 | 4.84 |

Source: Mid-Century Alaska, U.S. Dept. of the Interior, Office of Territories, U.S. Government Printing Office, Washington, D.C., 1952.

in much of the world this simple substance influences the whole manner of life of a people, even to survival.

The cold environment has a marked effect on water procurement. For many regions and for much of the year melted snow or ice is the chief source of water in rural regions. Quantity and quality thus depend on abundance and purity of ice, and on the available fuel to melt it. During the summer, permafrost serves the useful function of holding surface water in tundra areas, but at the same time creates significant and unique problems. For all practical purposes, available water is limited to surface sources; drilling of wells through the frozen ground is prohibitively expensive. Many tundra ponds

as —30° F., efficiency decreases below that level, until prolonged outdoor activity virtually ceases at —60° F. The bulky clothing[94] required at such extremes accounts for much of the reduced efficiency.

A number of studies on basal metabolic rates of Eskimos and presumably acclimatized white soldiers[16,42,69] have given results suggesting significantly higher rates for Eskimos. When both groups were on the same diet basal metabolic rates were within accepted normal limits for young white males. Generalizations about Eskimo diet are to be avoided[12], but the proportion of protein and fat consumed by natives under natural circumstances is probably more than in European diets. In-

creased heat production in Eskimos thus appears largely a function of diet.

Despite evidence of a peripheral vascular mechanism giving increased tolerance to cold[16], inherent racial peculiarities probably are not significant among explanations of why Eskimos get along better in cold climates than do whites. Rodahl[69] asserts that regardless of acclimatization, the success of arctic living and of survival in the cold depends mainly on three factors: know-how, environmental protection, and diet. Arctic living need not be unduly hazardous or even arduous for any group, regardless of genetic or environmental background.

*Effect of Physical Environment on Infectious Agents.* Cold has a demonstrated influence[88] on infectious agents of disease. Many bacterial and viral agents withstand prolonged cold, and often survive in greater numbers than at body temperature. These conclusions are substantiated for certain salmonellae and shigellae[6,29a,83], which can be recovered weeks or months after exposure to temperatures less than 0° C. The same holds for resistance to cold of *B. pestis*, *C. botulinus*[50], *Streptococcus fecalis*, and various spore formers[21]. Certain coliform bacteria and enterococci[26a] have been found viable after exposure at −21° C. during 2 years.

*E. histolytica* cysts, preserved in 5% glycerol were recovered after many weeks at — 79° C.[28]; in feces, salt solution[38] or distilled water, cyst survival was restricted to a few days at temperatures below freezing, although recovery was possible after 2 months at 0° C.[14].

**Biologic Environment.** With the biologic environment of human populations interpreted as all living things other than man himself, health relationships center on three main considerations. The first is the adequacy with which the environment provides man with a satisfactory food supply. The second is the significance of animal species as a reservoir of infection. The third is the part played by arthropods in transmission of infectious agents from man to man, or from animal reservoir to man.

*Food Supply.* Two aspects of the arctic climate combine to reduce agricultural potential. The first is low precipitation[77,81a]; cold air has a restricted capacity to carry moisture, Table 6. The second factor is the short growing season[81b], also a function of cold. For most plants of the Far North, duration of frost-free days and summer temperatures[55] are more important than winter extremes. And in the end, survival of all animals depends on nutrients drawn from plants.

The Arctic unlike most other parts of the world is without a grain staple such as rice, wheat, or maize, although northern Scandinavia and restricted regions of subarctic North America have profitable farming on a small scale, often combined with dairying. The principal crops are potatoes, cabbage, oats, and barley. Currently Alaska imports about 85% of needed foodstuffs, although with proper training, financing, and marketing[81b] a much larger proportion could be supplied locally. The Soviet Far North also imports large quantities of food, but agricultural productivity is reported to have improved in recent decades[85a].

Two animals, caribou and reindeer, convert the meager arctic forage into food, clothing, and shelter for many indigenous peoples; and reindeer provide transport as well[22,62]. Reindeer[85a] are the principal reliance in the Eurasian Arctic, caribou in North America. Some 60 years ago, reindeer were transplanted to Alaska and reached maximum numbers of about 630,000 in 1932. Due to overgrazed ranges and poor herding practices[47,74] the number had

dropped to about 25,000 in 1950. Caribou are the most widely distributed large land animal above the North American Arctic Circle, and seem to be holding their own[9]. They are an important part of the native economy.

In addition to caribou and agriculture, the land in Alaska also contributes wild berries and greens[39], eaten raw or preserved. Rabbit and ptarmigan are available, and mink and muskrat[45c] also serve as food, although trapped primarily for fur.

The sea supplies much of the food throughout the Arctic: fish in Norway, southwest Alaska and West Greenland; and sea mammals including walrus, whale, seal and polar bear along the Arctic Ocean[23] and North Greenland.

*Animal Reservoirs of Infection.* Throughout the North American Arctic dogs are still the chief means of winter transport; in many Alaskan villages[45c] they outnumber the human population. Dogs have had attention as a reservoir of human enteric pathogens[82] particularly salmonellae[1,8,29b,30,92]. Evidence of a similar role for *S. typhosa* is sketchy[43]. A recent survey[36] of dogs and man at Barrow, Alaska, resulted in isolation of *S. typhimurium* from some 12% of 149 people and 7% from 86 dogs. Dogs also act as a reservoir of infection in echinococcosis, diphyllobothriasis and rabies[65b]. Their numbers and close association with man have special significance in the arctic environment.

Diphyllobothriasis, the fish tapeworm disease of man, has interest because of animal reservoirs and a potential contribution to knowledge of transmission mechanisms in enteric disease of the Arctic, especially the part played by contact. The adult worm is harbored by man, bears, foxes, dogs and many fish-eating birds. Intermediate hosts are red salmon, smelt, blackfish and whitefish, which are variously eaten fresh and uncooked. Other features of the biologic environment enter into causation, for the larval stage has copepods as its primary host[65b,65c]. The disease is frequent in south Finland, but to what extent in Arctic parts of that country is undetermined. The few population surveys in Alaska give a prevalence of 15% or less[40a,40b], with again little knowledge of the situation in the true Arctic and Subarctic.

*Arthropod Vectors.* Arctic regions have a wide variety of arthropods[77] including lice, sandflies, black flies, deerflies, nonbiting flies and some 30 species of mosquitoes. Stefansson writes: "Though perhaps not impossible, it is difficult to exaggerate by words the number of mosquitoes you find in suitable arctic localities." In mid-summer, biting insects dominate the Arctic scene. None are known to transmit disease to man. They do affect morale, efficiency and comfort[91]. The significance of nonbiting flies in transmission of intestinal infection[6] is ill defined.

**Social Environment.** The causes of mass disease in man are resident in substantial degree in man himself. They relate to innate physical and psychical constitution; to intrinsic characters of age, sex and race; to resistance and susceptibility acquired through contact with his environment; and to natural resistance through genetic heritage. Disease also occurs because of the things he does, the beliefs he holds, his manner of life, and the nature of his associations with other men; this is the social environment.

The dominant culture differs materially in different parts of the Arctic. The influence of indigenous residents generally is more marked in North America than in Eurasia, where they are greatly in minority among nationals of the given country.

*Disposal of Wastes.* Some of the difficulties in practice of waste disposal and general sanitation relate to permafrost[32]. The digging of pits for privies and refuse requires an amount of labor that acts against their ready acceptance. In some arctic areas even burial of bodies awaits the spring thaw; old surface caskets are still in the cemetery behind the village of Barrow, Alaska. Privies are seen occasionally in rural Alaska but use is seemingly at a lesser frequency especially in winter when drifting snow and subzero temperatures reduce their attractiveness. In Scandinavia, where permafrost is not a consideration, essentially every dwelling has its outside privy, commonly a part of the barn to give protection.

Many Alaskan coastal villagers collect accumulated trash, feces and wastes in empty oil drums, and towards summer place them on the sea ice. The annual spring thaw or "break-up" carries the material away. In tundra and delta villages not enjoying the cleansing benefits of the ocean, disposal customarily consists of emptying the commode outdoors. The extreme cold may condone disposal of the contents in the vicinity of dwellings. It scarcely explains the indoor position of the open pail serving as commode, once seen near the stove and side by side with a similar receptacle holding the rising bread.

During winter months the accumulated wastes freeze and periodically are covered by fresh layers of snow. Many enteric pathogens are known to withstand prolonged freezing temperatures. When the spring thaw releases them, the community dosage is potentially great, aided as it is by the contribution of the dog population. Most Alaskan Eskimo villages experience annual spring and summer outbreaks of diarrhea, with periods of relative quiescence during winter, a situation that holds generally in the Arctic[75,87]. This seasonal periodicity suggests a relation to the cycles of freezing and thawing, alternately preserving and releasing intestinal pathogens. Serious deficiencies in environmental sanitation of essentially equal degree characterize both Arctic and Tropics; the main difference is that in the Arctic nature gives some relief during the cold part of the year, while the resident of the Tropics puts up with it all the time.

*Personal Cleanliness.* Recent studies in California[41,78] show that inadequate amounts of water for personal and environmental cleanliness have a bearing on the frequency of shigellosis. Limited water supply characterizes the Arctic, particularly Alaska. In Finnish Lapland, however, every household has its sauna, or steam bath, which itself is conserving of water.

The Eskimo in general appreciates differences in quality of water, with rain collected in summer the choice for drinking, and river or pond serving other needs. Less discrimination is shown in storing supplies indoors, the usual receptacle being a drum by the stove, frequently replenished but seldom cleaned.

*Housing.* A generalization about housing in the Arctic is that quarters are small in the interest of conserving heat. Living is crowded which favors contact infection and household transmission of disease.

About one-half of the houses in established villages of arctic Alaska[68] are of frame construction, many of logs and a considerable number are built of earth and sod. The usual abode is single story and of a basic pattern. An entrance vestibule devoted to storing tools and implements leads to a second vestibule used for food supplies, skins and perishables, both unheated. The main living quarters just beyond ordinarily are of one room, sometimes

two. The number of occupants is commonly five and may extend to ten or more. Snow igloos in truly polar regions, tents of skin or canvas, and conglomerate structures of waste metals, wood and other handy materials fill the need for temporary housing at fish camps, muskrat camps and in expeditions from the village[45a]. That so many live in such simple structures is not startling, for somewhere around half of the world is housed in mud huts.

Scandinavia and Russia have modern cities within the Arctic Circle, Murmansk being the metropolis with a population of 160,000 in 1940. Sweden lays claim in Kiruna to the largest city in the world, arctic or otherwise, with an area sufficient to accommodate London, New York and a few dozen others; the population is 18,000. These cities and many more tend to match the more populous centers to the south in type of dwelling and facilities, including electricity, telephone, central water supply, paved streets and other amenities. The farm houses of the Scandinavian North are not regularly aggregated into villages but each is on its own piece of land with appropriate outbuildings; and all painted a warm and cheery red. Most are of two stories. The older are built of logs and timbers but the majority are of frame construction in the pattern of the south. The general effect is that of Minnesota, to which so many of the people of these countries have gone.

*Population Mobility.* Lapps are a semi-nomadic people shifting widely with the seasons as required by reindeer farming. To an extent this holds also for the Eskimos because of fishing, hunting and trapping. Local movement of the general population in the Scandinavian North is favored by good transport according to arctic standards: railroads, bus lines and along the coast a system of small steamers, as in Greenland. The airplane has an established place in recent years. The work of the day is still by dog team in North America, by reindeer sled in Scandinavia, and both serve in various parts of arctic Russia.

The Arctic is no longer the isolated region it once was. A summer tourist business to the Norwegian North Cape by airplane and ship is well established. There is a start in Alaska, to Nome and Point Barrow. People move around more, both natives and outlanders. The opportunities for contact infection increase.

**Acute Intestinal Infections in Arctic and Subarctic.** Available data on the frequency of salmonellosis, shigellosis and amebic dysentery in arctic and subarctic areas are hopelessly incomplete; and by all that can be judged, the level of reliability is low. Many factors are responsible. The geographical remoteness of these parts of the world, language barriers, cultural misinterpretations, migration of the people, meager facilities for medical care and ill-developed means for reporting, are some of the reasons for existing deficiencies. The situation is by no means peculiar to the Arctic.

Even in military practice where reporting is as good as in any social group of the day, Gordon[33d] was unable to overcome the vagaries of clinical classification, and ended up by lumping the whole together as "the diarrheas and the dysenteries." Information on general populations of temperate zones is little better[20] and in the tropics perhaps not as good, if for no other reason than that of more cases to count.

One generalization seems definite: that the world over, the amount of infectious diarrhea is greater than routine reports show. A recent survey of bacillary dysentery in a rural community in Serbia[76] gave a frequency five times greater than officially recorded.

As health services improve and the level of medical care rises, the number of cases of unclassified diarrhea tends to decrease[18] and the proportion of specific infections to increase. No country, however, would seem to have information on salmonellosis, shigellosis and amebic dysentery comparable in validity to that of most reportable diseases, and the shortcoming of all morbidity reporting is recognized. Arctic and subarctic areas suffer particularly.

*Alaska.* That Alaska from time to time has had intestinal infection in epidemic proportion is definite. Watkins[84], a medical officer on an American ship cruising in Alaskan waters in 1913 noted that water supplies of the Eskimos were invariably polluted; of 281 illnesses that he treated, 35 were gastrointestinal infections. A more general survey of sanitary conditions[44] in Alaska of the same date stressed the role of person to person contact in transmission of disease, brought about by the "crowded, unventilated homes, where all eat out of the same dish, drink from the same teapot spout, use the same towel, and expectorate on the floor."

The history of the Territory is replete with dramatic and sometimes terrifying epidemics[37] which, of course, include the specific intestinal infections. An outbreak in 1807 in Unalaska is one of the first to be reasonably authenticated on epidemiological evidence as bacillary dysentery. Outbreaks of typhoid fever and dysentery were frequent during the Klondike gold rush of 1897. As recently as 1944 an epidemic of bacillary dysentery in the Kuskokwim area resulted in 97 deaths[60]. An epidemic of typhoid fever limited to children occurred in Spenard in 1951[31]. During 1948 an outbreak in the Barrow area[60] resulted in 105 cases and one death over a 5-month period; the infectious agent was *Shigella paradysenteriae.*

A localized outbreak of July, 1949, at Anaktuvak Pass[65a,65c] in the Brooks Range illustrates a typical circumstance. A camp of 70 Eskimos had had no determinable experience with epidemic diarrhea or dysentery. A young man arrived from Fairbanks and within succeeding days the trouble started. New cases appeared each day, most persons of the camp were affected, and to such extent that there were no hunters. The food situation became critical. Drugs and medical supplies were flown in from Barrow, tinned food was supplied, hunters became available again, and the emergency ended with 19 persons having been under active treatment, the total infected remaining unknown, and 2 children died. The infectious agent was identified as *Shigella paradysenteriae.*

Official reports for the Territory of Alaska give 274 cases and 24 deaths from typhoid fever, paratyphoid fever, and salmonellosis during the whole of the period 1900 to 1952. The records for shigellosis are 340 cases and 110 deaths from 1937 to 1951. The Alaska Department of Health is aware of the inadequacies of the data and has stated that they represent trends rather than an accurate record. In some years indeed[2b], more deaths have been reported from typhoid fever than cases. A recent survey by the Graduate School of Public Health, University of Pittsburgh[3], concludes that "the officially recorded incidence of 'diarrhea' and enteritis and other gastro-intestinal infections is absurdly low. It can be accounted for only on the basis that the diseases are not reported; indeed, in most instances probably not diagnosed. A low prevalence of diseases in this category is simply incompatible with the primitive state of environmental sanitation in the native communities."

With information on intestinal infection through official report so evidently unreliable, attention turns to field surveys. Few such studies have been made. A general sickness survey[89] of the urban population of Anchorage in 1954 gave annual rates for gastroenteritis of 11.82 per 1,000 population compared with 0.72 for the city of Pittsburgh; the rate for ill-defined gastro-intestinal conditions was 13.46 in Anchorage and 0.82 in Pittsburgh. Haldeman[37] in discussing problems of Eskimos, Indians and Aleuts stated that "diseases spread chiefly through the discharges of the intestinal tract represent a major cause of morbidity in Alaska." The Anchorage data would support that. No systematic survey for carriers of bacterial intestinal pathogens has been made, other than recent unpublished data[7,26b] already referred to[36].

Two field surveys represent about all that is known of helminth and protozoal intestinal infection in Alaska. A rate of 3% was established for *E. histolytica* among Eskimos of the Bethel area[40b]. Examination of six serial fecal specimens from each of 100 Eskimos in Kotzebue[40a] failed to demonstrate that microörganism.

The true incidence of intestinal infection in Alaska, bacterial, protozoal or helminthic, is little better than a guess. That most of the common infectious agents are present seems demonstrated; knowledge has been enlarged since a public health laboratory service was established about 1936. Deaths from ill-defined causes are so numerous as to discount most disease-specific death rates, aside from the question of their individual reliability. Epidemiologic effort has been limited mainly to the study of epidemics, with the infectious agent commonly identified[90] but source of infection much less frequently. Poor water supply and sewage disposal are likely responsible for original infections[60], but the extent to which they act in propagation of an epidemic is less certain; central water supplies for one thing are uncommon. The endemic situation is indefinite, of itself and in relation to epidemics.

*Other Arctic Countries.* Official sources and published reports of intestinal infection in other parts of the Arctic and Subarctic have been searched with the same thoroughness as for Alaska. This includes Canada, Greenland and Iceland, the Scandinavian countries and the Soviet Union of Europe and Asia. This information has been enlarged by conferences with health officers in many of these countries. The accumulation led to essentially the result just set forth for Alaska. Further detailed recital of inadequate data seemingly serves no useful purpose.

What is known about intestinal infection in Arctic and Subarctic can be summed up in a few words. Most of the common pathogens, bacterial and parasitological, have been demonstrated to be present. Observations on water supply, sewage disposal and environmental sanitation suggest that incidence should be high. Reports of epidemics support this. Recorded morbidity and mortality have little worth as indices. Quantitative rates of frequency, seasonal prevalence, the situations that give rise to epidemics, and the relative significance of propagation by contact and vehicle are matters to be determined by visits to the homes of people and the field use of bacteriological methods.

**Field Studies on Intestinal Infection in Cold Climates.** A plan of study designed to give answers to some of the questions evident from this review is now presented. The primary objective is to define principle in origin and movement of disease in man as modified by the arctic environment. The

reason for choosing the common intestinal infections as the specific material for investigation has been given. The information acquired should be applicable to other major groups of infectious disease, thereby permitting still broader generalization.

The study includes surveys of whole populations at a fixed field station in winter and summer, with observation of both bacterial and parasitic intestinal pathogens; the evoluting epidemics that characterize the spring thaws; the study of chance outbreaks; and the search in summer months of general prevalence for areas of excess incidence and the responsible causes. Family case study is practiced in both endemic and epidemic situations.

The areas selected for study represent the several kinds of arctic environment. Populations of tundra country have been observed in the far north along the Arctic Ocean coastline of Alaska, latitude 70° N., and in the subarctic region of the Kuskokwim River, latitude 61° N. Studies currently are underway in the taiga region of Finnish Lapland, to be followed shortly by a survey in the relatively warm, wet coastal region of arctic Norway. Plans are projected for duplicate observations in the contrasting glacier country of Greenland.

All are rural areas, if such may be fittingly applied to the Arctic, chosen first because that is the typical Arctic and secondly because rural areas always give favorable opportunity to define principle in disease behavior. Cities are more frequently chosen because working conditions are easier, but cities the world over tend to run to type. The arctic countryside has other advantages.

The climate is relatively simple and mainly cold. Flora and fauna are also simple, compared with the lushness and diversity of the tropics. The people, too, are wholesome and simple but that is more a characteristic of rural regions than of the Arctic. The work was with Eskimo populations in Alaska, because aside from cities, that is the dominant element. Operations in Finland and Norway are in areas with only white nationals, because the indigenous Lapps are a minority.

The logistics of field studies in arctic regions introduce elements foreign to ordinary field operations, travel particularly. The distances are enormous. Alaska superimposed on the United States would stretch from Charleston, S. C., to San Diego, and from the Mexican border to Canada. Greenland is the largest island in the world. The possibilities of rail travel are few; airplanes are usual but from the last airport it is "bush" plane to a beach or ski landing. Local travel is by boat, reindeer sled or dog team, sometimes by foot and on occasion luxuriously by bus.

Laboratories have to be flown in to field headquarters a load at a time in the little planes and set up somewhere, the schoolhouse being a choice location. Basic services of electricity, gas and water are not to be expected.

For many weeks of the year darkness restricts outdoor activities to a few hours a day, but the summer working day has no limitations in the land of the midnight sun. Bad weather may suspend operations for days, and a whale feast has had the same result. Cold is the common and enduring concern, as it affects housing, person, and even specimens sent out to the base laboratory. There is still opportunity for pioneering in field epidemiology, and the yield is rewarding.

UNIVERSITY OF MICHIGAN LIBRARIES

REFERENCES

(1) **Adler, H. E., Willers, E. H.,** and **Levine, M.:** J. Am. Vet. Med. Assn., **118,** 300, 1951. (2) Alaska Department of Health: (a) Alaska's Health, **12,** 7, 1955; (b) Personal communication, Bureau of Vital Statistics, November 2, 1954. (3) Alaska Health Survey Team: Alaska's Health: A Survey Report to the United States Department of the Interior, Pittsburgh, Graduate School of Public Health, 1954. (4) **Alter, A. J.:** Nordic Health Notes, Proc. 2nd Alaska Science Conference, Alaska Division, Am. Assn. Adv. Sci., 1951. (5) Annual Report from the Chief Medical Officer in Greenland, 1953. (6) Army Environmental Health Laboratory: Final Report: Human Wastes in Arctic and Sub-Arctic, 1955.

(7) **Babbott, F. L., Jr.,** and **Gordon, J. E.:** Unpublished data. (8) **Ball, M. R.:** J. Am. Vet. Med. Assn., **118,** 164, 1951. (9) **Banfield, A. W. F.:** The Barren-Ground Caribou, Ottawa, Dept. of Resources Northern Administration and Lands Branch, 1951. (10) **Barnett, L.:** The Arctic Barrens: The World We Live In, Life Magazine, 1955. (11) **Brewer, M. C.,** and **MacCarthy, G. R.:** Geothermal Fluctuations in Permafrost at Point Barrow, Alaska. Proc. 3rd Alaskan Science Conference, Alaska Division, Am. Assn. Adv. Sci., September, 1952. (12) **Brown, G. M.:** Metabolic Studies of the Eskimo. Cold Injury: Trans. of 3rd Conference, Feb. 22, 23, 24, 25, 1954, edited by M. Irené Ferrer, New York: The Josiah Macy, Jr. Foundation.

(13) Canada Department of Mines and Technical Surveys: An Introduction to the Geography of the Canadian Arctic: Canadian Geography Information Series No. 2, Ottawa, 1951. (14) **Chang, S. L.:** A Final Report on the Survival of Cysts of *Endamoeba histolytica* in Human Feces Under Low-Temperature Conditions. Annual Report, Commission on Environmental Hygiene, Armed Forces Epidemiological Board, 1953–54. (15) **Christensen, P. E., Schmidt, H., Jensen, O., Bang, H. O., Andersen, V.,** and **Jordal, B.:** Acta med. Scandinav., **144,** 313, 1952. (16) **Coffey, M. F.:** A Comparative Study of Young Eskimo and Indian Males with Acclimatized White Males. Cold Injury: Trans. of 3rd Conference, Feb. 22, 23, 24, 25, 1954, edited by M. Irené Ferrer, New York, The Josiah Macy, Jr. Foundation. (17) **Collinder, B.:** The Lapps, Princeton: Princeton Univ. Press, 1949. (18) **Cooper, M. L., Furcolow, M. L., Mitchell, A. G.:** and **Cullen, G. E.:** J. Pediat., **15,** 172, 1939.

(19) **Dunbar, M. J.:** Arctic, **7,** 27, 1954.

(20) **Edge, P. G.:** Vital Statistics and Public Health Work in the Tropics, London: Bailliere, Tindall and Cox, 1947. (21) Editorial: Effect of Cold on Micro-Organisms, Nature, **168,** 990, 1951. (22) **Ekvall, S.:** Acta med. Scandinav., **105,** 329, 1940.

(23) **Ferris, B. G., Jr.:** Survey of Some Aspects of Human Ecology of the Pond Inlet Area, Northwest Territory, Canada. Report on Expedition to Bylot Island, Franklin District, North West Territories, Canada, June 13–July 31, 1954. Boston: Harvard School of Public Health, Dept. of Physiology, 1954. (24) Finnish State Medical Board: Personal communication, 1955. (25) **Fodor, E.,** Ed.: Scandinavia, 1955. New York: McKay Co., Inc., 1955. (26) **Fournelle, H. J.:** (a) Effect of Low (near- and sub-freezing) Temperatures on the Viability of Certain Pathogenic and Non-Pathogenic Enteric Bacteria and of the Effect of Several Factors. Washington: Dept. of Health, Education and Welfare, Public Health Service, 1955; (b) Unpublished data. (27) **Friedmann, K. J.:** Current Transition in the Economy of Greenland. Washington: Office of Naval Research. (28) **Fulton, J. D.,** and **Smith, A. U.:** Ann. Trop. Med., **47,** 240, 1953.

(29) **Galton, M. M.:** (a) Poultry Diseases Transmissible to Man. Jacksonville, Florida State Board of Health; (b) Salmonella Infections and their Relation to Public Health, Chap. X in Advances in Veterinary Science, New York: Academic Press, 1953. (30) **Galton, M. M., Scatterday, J. E.,** and **Hardy, A. V.:** J. Inf. Dis., **91,** 1, 1952. (31) **Gaub, W. H.:** J. Lab. & Clin. Med., **37,** 931, 1951. (32) **Glennen, E. J.:** Design and Construction in Permafrost Regions. Proc. 3rd Alaskan Science Conference, Alaska Division, Am. Assn. Adv. Sci., 1952. (33) **Gordon, J. E.:** (a) Am. J. M. Sci., **215,** 311, 1948; (b) Ecologic Investigation of Disease, in Research in Public Health. New York: Milbank Mem. Fund, 1952; (c) J. Roy. San. Inst., **74,** 445, 1954; (d) A History of Preventive Medicine in the European Theatre of Operations. U. S. Army, 1941–45, Washington: Dept. of Army, Off. of the Surgeon General, 1948. (34)

**Gordon, J. E.,** and **Augustine, D. L.:** Am. J. M. Sci., **216,** 343, 1948. (**35**) **Gordon, J. E., Wyon, J. B.,** and **Ingalls, T. H.:** Am. J. M. Sci., **227,** 326, 1954. (**36**) **Grumbles, L. C.,** and **Maciolek, J. A.:** The Isolation of Enteric Pathogens from Humans and Dogs at Barrow, Alaska. Presented at the 6th Annual Alaska Science Conference, Fairbanks, Alaska, June, 1955.

(37) **Haldeman, J. C.:** Pub. Health Rep., **66,** 912, 1951. (**38**) **Halpern, B.,** and **Dolkart, R. E.:** Am. J. Trop. Med. & Hyg., **3,** 276, 1954. (**39**) **Heller, C. A.:** Alaska's Health, **6,** 7, 1948. (**40**) **Hitchcock, D. J.:** (a) J. Parasitol., **36,** 232, 1950; (b) Ibid., **37,** 309, 1951. (**41**) **Hollister, A. C., Beck, M. D., Gittelsohn, A. M.,** and **Hemphill, E. C.:** Am. J. Pub. Health, **45,** 354, 1955. (**42**) **Horvath, S. M., Freedman, A.,** and **Golden, H.:** Am. J. Physiol., **150,** 99, 1947.

(43) **Krogh-Lund, G.:** Compt. rend. Soc. de biol., **105,** 615, 1930. (**44**) **Krulish, E.:** Pub. Health Rep., **28,** 544, 1913.

(45) **Lantis, M.:** (a) Present Status of the Alaskan Eskimo, in Selected Papers of Alaskan Science Conference, 1950, Ottawa, Arctic Institute of North America, 1952; (b) An Essay on Research in the Human Ecology of the American Arctic in Recent Years, mimeographed, Arctic Institute of North America, 1953; (c) Unpublished data, 1955. (**46**) **Lappo, S. D.:** Spravochnaya Knizhka Polyarnika, p. 341, 344–352, 1945, cited by Webster[85a]. (**47**) **Leopold, A. S.,** and **Darling, F. F.:** Wildlife in Alaska. New York: Ronald Press, 1953. (**48**) **Lloyd, T.:** J. Geography, **49,** 319, 1950. (**49**) **Loree, D. R.:** Northwest Med., **34,** 262, 1935. (**50**) **Luyet, B. J.,** and **Gehenio, P. M.:** Life and Death at Low Temperatures, Biodynamica, 1940.

(51) **Marchand, J. F.:** J. Am. Med. Assn., **123,** 1019, 1943. (**52**) **Mills, C. A.:** Medical Climatology. Springfield, Ill.: Charles C Thomas, 1939. (**53**) **Muller, S. W.:** Permafrost or Permanently Frozen Ground and Related Engineering Problems. Ann Arbor, Mich.: J. W. Edwards, Inc., 1947.

(54) New York Times: Science Against the Arctic, April 12, 1955. (**55**) **Nordenskjöld, O.,** and **Mecking, L.:** The Geography of the Polar Regions, New York: American Geographical Society, 1928. (**56**) Norwegian Ministry of Social Affairs, Health Services of Norway: Personal communication, 1955.

(57) **Pampana, E. J.,** and **Russell, P. F.:** Malaria: A World Problem. Geneva, World Health Organization, 1955. (**58**) **Panum, P. L.:** Observations Made During the Epidemic of Measles on the Faroe Islands in the Year 1846, New York: Am. Pub. Health Assn., 1940. (**59**) **Paul, J. H.,** and **Freese, H. L.:** Am. J. Hyg., **17,** 517, 1933. (**60**) **Pauls, F. P.:** Pub. Health Rep., **68,** 531, 1953. (**61**) **Polunin, N.:** Am. Scientist, **43,** 307, 1955. (**62**) **Porsild, A. E.:** Land Use in the Arctic. Proc. 2nd Alaskan Science Conference, Alaska Division, Am. Assn. Adv. Sci., 1951. (**63**) **Powers, W. E.:** J. Geography, **49,** 186, 1950.

(64) Rand McNally—Cosmopolitan World Atlas. Chicago, Rand McNally & Co., 1951. (**65**) **Rausch, R.:** (a) Arctic, **4,** 147, 1951; (b) Animal-borne Diseases in Alaska and their Public Health Significance, Proc. 15th International Veterinary Congress, Stockholm, Sweden, Aug. 9–15, 1953; (c) Unpublished data, 1955. (**66**) Report on Greenland, 1954; Copenhagen, The Greenland Department, 1954. (**67**) Report of Technical Assistant to Chief of Naval Operations for Polar Projects: Low Temperature Sanitation, June, 1954. (**68**) Report No. 2503, U. S. House of Representatives, Washington, U. S. Government Printing Office, 1953. (**69**) **Rodahl, K.:** North. New York: Harper & Brothers, 1953. (**70**) Royal Danish Ministry for Foreign Affairs: Greenland. Copenhagen.

(71) **Sanders, I. T., Woodbury, R. B.,** and **Schwendeman, J. R.:** Societies Around the World. New York: Dryden Press, 1953. (**72**) **Schwalbe, A. B.:** Dayspring on the Kuskokwim. Bethlehem, Pa.: Moravian Press, 1951. (**73**) **Shelesnyak, M. C.:** The Arctic as a Strategic Scientific Area. Joint Seminar of the Arctic Institute of North America and the Isaiah Bowman School of Geography, the Johns Hopkins University, May 25, 1950. (**74**) **Skarland, I.:** Economic, Social and Anthropological Problems in Alaska. Proc. 2nd Alaskan Science Conference, Alaska Division, Am. Assn. Adv. Sci., 1951. (**75**) **Smirnov, I. I.:** Khnicheskaiâ meditsina, **25,** 73, 1947, abstracted in Arctic Bibliography, **4,** 989, 1954. (**76**) **Snajder, K.:** Bull. World Health Org., **10,** 77, 1954. (**77**) **Stefansson, V.:** Arctic Manual, New York: Macmillan Co., 1953. (**78**) **Stewart, W. H., McCabe, L. J., Jr., Hemphill, E. C.,** and **DeCapito, T.:** Am. J. Trop. Med. & Hyg., **4,** 718, 1955. (**79**) **Strode, G. K.:** Yellow Fever. New York: McGraw-Hill Book Co., 1951. (**80**) Swedish Medical Board: Personal communication, 1955.

UNIVERSITY OF MICHIGAN LIBRARIES

(81) United States Dept. of the Interior: (a) Mimeographed data compiled by Office of Indian Affairs, Field Service, Juneau Alaska, March 30, 1938, pp. 1–16; (b) Mid-Century Alaska, Washington, U. S. Government Printing Office, 1952.
(82) **Varela, G., Perez-Rebelo, R.,** and **Olarte, J.:** J. Am. Vet. Med. Assn., **119,** 385, 1951.
(83) **Wallace, G. T.:** The Longevity of Salmonella and Shigella Species and *E. coli* in Human Feces Exposed to Low Temperatures. Progress Report to Armed Forces Epidemiological Board, March, 1954. (84) **Watkins, J. A.:** Am. J. Pub. Health, **4,** 643, 1914. (85) **Webster, C. J.:** (a) Arctic, **4,** 27, 1951; (b) Ibid., **7,** 59, 1954. (86) Webster's New International Dictionary, 2nd ed. Springfield, Mass.: G. & C. Merriam Co., 1948. (87) **Wegman, M. E.:** Yale J. Biol. & Med., **25,** 358, 1953. (88) **Weiser, R. S.,** and **Osterud, C. M.:** J. Bact., **50,** 413, 1945. (89) **Weiss, E. S.:** Sickness Survey, Anchorage. (unpublished data). (90) **Williams, R. B.:** Northwest Med., **49,** 340, 1950. (91) **Wilson, C. S.:** The Status of Mosquito Control in Alaska—Civilian Aspects, Proc. 3rd Alaskan Science Conference, Alaska Division, Am. Assn. Adv. Sci., 1952. (92) **Wolff, A. H., Henderson, N. D.,** and **McCallum, G. L.:** Am. J. Pub. Health, **38,** 403, 1948. (93) World Almanac: ed. by H. Hansen. New York World-Telegram, 1954.
(94) **Yaglou, C. P.:** Habitability Studies in Climatic Extremes, Ann. Rep. to Commission on Environmental Hygiene, Armed Forces Epidemiological Board, Washington, April 1, 1954.

# PHYSIOLOGY

PROCEEDINGS OF

## The Physiological Society of Philadelphia

SESSION OF NOVEMBER 15, 1955

### INFORMAL SEMINAR ON RECENT ADVANCES IN CARDIOLOGY

**Introductory Remarks.** M. J. OPPENHEIMER, M.D. (Temple University of Medicine). Mr. President, Members of the Society: it is a privilege to have been asked to preside over this panel which demonstrates the correlation between clinical and basic science fields. Doctor Seiden will demonstrate, in a very fundamental approach, the validity of the "dipole hypothesis" of electrocardiography which is so widely used in the clinical application of the electrocardiogram. Dr. J. J. Sayen has already published myocardial maps for reconstructing, correlating and illustrating data obtained from the electrocardiogram and postmortem data which aid in localization and interpreting cardiac disease. He has also shown that oxygen saturation of blood need not be a measure of oxygen tension and hence availability at the infarct. In the light of the recent illness of the President of the United States this is of foremost interest to us now. He will correlate oxygen availability and electrocardiographic changes at the infarct. Dr. Bellet's Heart Clinic at Philadelphia General Hospital is known to most of us. However, here the clinician will deal with such basic terms as increases in pacemaker rhythmicity due to sodium lactate which are useful in cardiac standstill and will speak of increased conductivity in the myocardium due to the same agent. What better junction of basic and clinical science could be sought? Finally, Dr. Thomas M. Durant, although a Clinical Professor of Medicine, has been an outstanding leader in research on the pathophysiology of disturbances in the cardiovascular respiratory system in gas embolism. He will report on a technique of image amplifier cinefluorography which has a wide potential field of clinical and physiological use.

**Quantitative Approach to Electrocardiographic Theory: The Normal and Abnormal QRS Complex.** GEORGE E. SEIDEN, M.D. (Robinette Foundation, Hospital of University of Pennsylvania). Electrocardiographic theory can be divided into three categories: The study of 1) generation of bioelectric potential across cell membranes, 2) details of spread of depolarization and repolarization in heart muscle, 3) distribution of body surface potential.

Our group (Drs. Frank, Kay, Keisman and the author) has studied body surface potential, first in a model with resistive homogeneous interior and internal fixed-location dipole current source, and secondly in the human from whom the model was formed. Model studies revealed marked influence of dipole location and boundary form on surface potentials, which could be quantitatively depicted on geometric constructions called image surfaces.

Studies in the human were as follows: 1) By a precision 4-electrode cancellation technique, existence of mirror patterns was demonstrated for any body surface QRS complex, establishing that ventricular depolarization could be



UNIVERSITY OF MICHIGAN LIBRARIES

represented as a single fixed-location dipole. 2) Study of cancellation data at heart level enabled anatomic location of the equivalent dipole in the human subject, and measurement of dipole components. 3) By using these dipole components and model data representative of the subject's dipole location, wave shapes of numerous bipolar and unipolar QRS complexes were calculated for many sites on the human and compared with actually measured QRS complexes. Agreement was striking.

Studies were extended to cardiac patients. The four-electrode cancellation technique was applied to 60 patients with characteristically abnormal QRS complexes, demonstrating that ventricular depolarization in patients is represented by a fixed-location equivalent dipole with accuracy of 80% or better. By matching patient heart level transverse plane cancellation data to similar model data characteristic of various dipole locations, the electric heart center for the QRS was located in 40 patients to be in 93% of cases in a 5 cm.-square area forward and to the left in the transverse plane.

Finally, with the above data helping to establish design requirements, an orthogonal lead system for vectorcardiography, called the precordial system, has been developed and is in process of evaluation.

**Studies of Experimental Localized Myocardial Ischemia with Special Reference to its Epicardial Electrocardiographic Reflection and to Intramyocardial Temperature Changes.** JOHN J. SAYEN, M.D., WARNER F. SHELDON, M.D., and GEORGE PEIRCE, M.S. (Departments of Medicine and Pathology, University of Pennsylvania, Philadelphia, Pennsylvania). Following occlusion of medium-sized coronary arterial branches in dogs, significant epicardial electrocardiographic abnormality has not been seen for 25 to 50 heart beats (12 to 30 seconds). RS–T segment elevation then appears and the inverted T–waves characteristic of exposed hearts simultaneously begin reversal of direction, steadily increasing in positivity. Polarographic oxygen tension, myocardial electrocardiograms, and muscle contraction (motion picture analysis) show abnormality within 10 heart beats. Acute coronary narrowing sufficiently severe to disturb measurably these more sensitive indices of ischemia produces significant epicardial electrocardiographic abnormality late, if at all.

Raising ventricular surface temperature 0.5° C. reverses the negative T–waves of exposed hearts (and superficial intramyocardial T–waves). The change begins immediately and is complete within a few heart beats. Heart surface cooling produces equally prompt, opposite effects. Hearts warmed enough to produce positive left ventricular T–waves have not shown epicardial electrocardiographic changes following coronary occlusion sooner than hearts exposed to room air.

Intramyocardial temperature measurements have been obtained from a thermistor mounted in a hypodermic needle, by measuring the degree of unbalance of a Wheatstone bridge; the sensitivity usually employed being 0.0161° C. per millimeter of galvanometer scale. In exposed hearts, muscle temperatures may be 1 to 2° C. below the left ventricular blood. As intrathoracic temperature approaches blood temperature, the left ventricular wall becomes 0.2 to 0.5° C. warmer than its blood.

The direct effects of coronary occlusion on intramyocardial temperature vary greatly with blood, ventricular muscle, and intrathoracic temperatures; but have been too delayed, even in exposed hearts (10 to 20 seconds), to

affect T-wave amplitude prior to the onset of RS–T segment elevation. In hearts warmer than their blood, especially when intrathoracic temperature closely approximates blood temperature, coronary occlusion may not drop temperatures in an ischemic area for 30 to 60 seconds. The earliest change may be a temperature rise. This latter circumstance should, if anything, increase local T-wave positivity. Increased negativity of epicardial T-waves following coronary occlusion has not been seen under conditions where temperature artefacts could be excluded.

**Effect of Molar Sodium Lactate in Increasing Cardiac Rhythmicity: Its Use in the Treatment of Slow Heart Rates, Stokes-Adams Syndrome and Episodes of Cardiac Arrest.** SAMUEL BELLET, M.D., FRED WASSERMAN, M.D., and JEROME I. BRODY, M.D. (From the Harrison Department of Surgical Research, University of Pennsylvania). The effects of molar sodium lactate on cardiac rhythmicity has been studied in dogs with complete A–V heart block, slow idioventricular rhythm and cardiac arrest, produced by obstructive asphyxia, severance of the A–V node, and toxic doses of Nembutal. Similar studies were made in patients with Stokes-Adams syndrome, cardiac arrest, partial and complete A–V heart block, sinus bradycardia and other arrhythmias. The molar lactate was successful in restoring cardiac beating in patients with cardiac arrest when administered during a critical period. In the presence of Stokes-Adams attacks, the infusion was successful in restoring ventricular beating on numerous occasions.

In patients with sinus bradycardia and partial and complete A–V heart block, the idioventricular rate was significantly increased. In one of these, where the control rate was 15 per minute with no obtainable blood pressure, the solution increased the ventricular rate to 60 per minute, within a period of 4 minutes. After 5 hours of administration, the complete A–V heart block was restored to a partial A–V heart block.

The solution manifested a paucity of untoward effects even when administered in large doses and to patients with severe grades of myocardial damage. Except for transient extrasystoles in 6 cases, there was no evidence of the dangerous types of ectopic rhythm as are observed following epinephrine.

Studies performed on the dog, where complete A–V heart block and cardiac arrest were produced, yielded similar results.

It is felt that the administration of molar and one-half molar sodium lactate is an important addition to the therapy of cardiac arrest and slow ventricular rates. The exact mechanisms by which these changes occur are being investigated at the present time. Preliminary studies suggest that the solution acts by increasing the rhythmicity of the cardiac pacemaker.

**Visualization of Intracardiac Structures with Gaseous $CO_2$.** T. M. DURANT, M.D., H. M. STAUFFER, M.D., and M. J. OPPENHEIMER, M.D. (Departments of Medicine, Radiology and Physiology, Temple University School of Medicine). Previously reported studies using biplane stereoscopic angiocardiography have demonstrated excellent visualization of intracardiac structures in the experimental animal when gas is used as the contrast medium. The introduction of the image amplifier (Philips), which brightens the fluoroscopic image 1000 times, has extended the possibilities in such visualization by allowing cinefluorography with demonstration of the dynamics of cardiac events. Carbon dioxide has been chosen for this study because of its high solubility and hence the lessened danger of embolic sequelae. This gas is well tolerated by animals despite repeated intravenous

UNIVERSITY OF MICHIGAN LIBRARIES

injection of 7.5 ml./kg. Its safety has been further demonstrated by the injection of similar amounts at the root of the aorta, into the left ventricle and into the cephalic end of the carotid artery. Slow motion projection of the moving picture film taken following the systemic venous injection of the gas shows very well the movements of the tricuspid and pulmonic valves as well as the contraction of the right ventricular chambers. Similar recording of events following injection into the left ventricle shows the movements of the aortic and mitral valves and contraction of the walls of this chamber. In one animal, passage of the gas from the left to the right atrium was demonstrated and subsequent necropsy confirmed the presence of an interatrial septal defect. In all experiments disturbances of circulation, respiration and gas contents (oxygen and carbon dioxide) of the blood are minimal. It is believed that carbon dioxide is a safe gas for visualization of intracardiac structures in a manner not possible by other means.

# BOOK REVIEWS AND NOTICES

PERSPECTIVES AND HORIZONS IN MICROBIOLOGY. Edited by SELMAN A. WAKSMAN. Pp. 220; 4 ills. New Brunswick, N. J.: Rutgers University Press, 1955. Price, $3.50.

THIS volume consists of the papers given at the dedication of the Institute of Microbiology at Rutgers University in June, 1954. Each author is an authority who prepared for the occasion a careful analysis of his subject. The result is gratifying. Each paper represents, to use a figure of speech, a distillate of a large body of knowledge purified by passage through the minds of active and able contributors.

The area encompassed by the thirteen authors is so broad that students of human biology and general biology alike will find rich reward for time spent in browsing. Of special interest to the medically minded are discussions of immunologic frontiers by Heidelberger, of viral chemotherapy by Horsfall, of antibiotic research by Eagle and of microbial genetics by Lederberg and by Davis. Reading these papers, some carefully and others casually, gave this reviewer the feeling of having sat through a top-notch review course which might have been entitled, "Present Trends in Microbiologic Research."

E. S.

---

PROCTOLOGIC ANATOMY. BY R. V. GORSCH, M.D., Clinical Professor of Proctology, New York Polyclinic Medical School and Hospital. 2nd ed. Pp. 310; 155 ills. Baltimore: Williams & Wilkins Co., 1955. Price, $8.00.

A WORKING knowledge of proctologic anatomy is perhaps the single most important factor in the success of operations on the rectum and anal canal. In 1941, Dr. Gorsch carefully consolidated in one volume the results of his dissections and outstanding studies in proctologic anatomy. This work quickly became a reference text to proctologists as it was the single work in proctology emphasizing anatomy in diagnosis, pathogenesis and surgical treatment of anorectal diseases.

The second edition of this text surpasses the first one. The entire material has been revised and brought up-to-date. Recent contributions to the anatomic literature particularly that of Uhlenhuth have added greatly to the value of the work. Dr. Gorsch has supplemented much of the text by his own anatomical knowledge thus enabling the reader to clearly understand certain of the more complex problems.

Dr. Gorsch has kept his text concise and has neatly avoided much of the controversy that exists among proctologic anatomists. This approach though by-passing much of the confusion found in the literature renders the text more readable and fulfills its main purpose which is the aiding of the surgeon actively engaged in practical operative management. It is expected that this edition will achieve even greater popularity than the first one.

H. T.

---

THE YEAR BOOK OF PATHOLOGY AND CLINICAL PATHOLOGY (1954–1955 Series). Edited by WILLIAM B. WARTMAN, B.S., M.D., Morrison Professor of Pathology, Northwestern University. Pp. 486; 168 ills. Chicago: Year Book Publishers, Inc. Price, $6.00.

THE current volume of this series contains abstracts of pertinent articles which appeared in various journals during the calendar year, 1954. Although a few important articles appear to have been overlooked, the over-all coverage of topics is excellent. In addition, there are valuable special articles including "Carcinoma in Situ," by J. W. Reagan; "Experimentally Induced Developmental Abnormalities of the Central Nervous System," by S. P. Hicks; and "Serum Sodium Concentration and Its Therapeutic Significance to the Clinical Pathologist," by W. S. Hoffman.

Pathologists and clinical pathologists will find this volume a helpful guide to reading in their fields of interest.

C. Z.

---

ANTIBIOTICS ANNUAL, 1954–1955. Edited by HENRY WELCH, PH.D., Director, Division of Antibiotics, Food and Drug Administration and FÉLIX MARTÍ-IBANEZ, M.D. Pp. 1150; illustrated. New York: Medical Encyclopedia, Inc., 1955. Price, $10.00.

THE second Annual Symposium on Antibiotics was held in Washington, October 25 to 29, 1954. Some 175 speakers were heard and the papers presented there comprise this volume. The bulk of the material is widely varied, concerned as it is with numerous antibiotics. While some discussion is devoted to the antibiotics currently in clinical use, there is also much information on substances still in the laboratory experimental



UNIVERSITY OF MICHIGAN LIBRARIES

stage. In addition, there are two excellent broad papers: "Historical Background of Antibiotics," by Selman A. Waksman; and "The Philosophical Impact of Antibiotics on Clinical Medicine," by Félix Martí-Ibañez.

This volume will be of obvious value to clinicians, bacteriologists, and others interested in infectious diseases and their treatment. C. Z.

---

INDUSTRY AND TROPICAL HEALTH II. Proceedings of the Second Conference of the Industrial Council for Tropical Health. Sponsored by The Harvard School of Public Health, April 20, 1954, in New York and April 21 and 22, 1954, in Boston. Pp. 266; illustrated. Boston: Harvard School of Public Health, 1955. Price, $10.00; professional rate, $5.00.

THE Second Industrial Tropical Health Conference was held in April, 1954, its first day's session in New York and the last two in Boston. This volume records the discussions of experts in Tropical Medicine on the problems of health as met and solved by industry in various tropical parts of the world. The book offers a wealth of first-hand new and practical information on the most important aspects of tropical medicine and from the most authoritative sources. The leading spirit in establishing these meetings was absent from this one, being already in his last illness. This volume and the records of future conferences will memorialize a great leader in this field, James Stevens Simmons. R. K.

---

DIE GRUNDLAGEN DER TRANSPLANTATION VON FREMDEM KNOCHENGEWEBE. BY DR. MED. WOLFGANG LENTZ, University of Kiel. Pp. 111; 69 ills. Stuttgart: Georg Thieme Verlag. 1955 (Intercontinental Medical Book Corp., New York, U. S. Agents). Price, $4.30.

THIS excellent booklet is highly recommended to all surgeons and orthopedists who are interested in transplantation of bone. The first 27 pages contain a comprehensive and critical review of the literature. The following 35 pages present the results of more than 500 dog experiments. Another 29 pages relate clinical experiences. In many cases such as fresh fractures any material (fresh or conserved auto-, homeo- or heteroplastic bone) was found to be useful, while in other cases such as pseudarthroses only biologically valuable bone (notably fresh autoplastic bone) could be transplanted successfully. Cooked or macerated bone gave poor results, while deep-cooling and conservation in serum or blood furnished biologically valuable transplants. W. E.

---

MECHANISMS OF MICROBIAL PATHOGENICITY. The Fifth Symposium of The Society for General Microbiology. Edited by J. W. HOWIE and A. J. O'HEA. Pp. 333; illustrated. New York: Cambridge University Press, 1955. Price, $5.00.

THE contributions in this volume were presented at the Fifth Symposium of The Society for General Microbiology held in London, April, 1955. The object of the symposium was to focus attention on the processes by which infecting organisms produce disorders of function or metabolism in host organisms. The range of the discussions is broad, with consideration of the pathogenicity of bacteria, fungi, and protozoa not only for man, but also for animals and plants.

Although anyone interested in the basic considerations of infectious diseases will find much of value in this volume, it is particularly recommended to bacteriologists, and to plant as well as animal pathologists. C. Z.

---

COLLECTED PAPERS OF THE MAYO CLINIC AND MAYO FOUNDATION, VOL. 46, 1954. Edited by RICHARD M. HEWITT, M.D., A. B. NEVLING, M.D., JOHN R. MINER, SC.D., JAMES R. ECKMAN, PH.D., M. KATHARINE SMITH, B.A., CARL M. GAMBILL, M.P.H., FLORENCE SCHMIDT, B.S.E., AND GEORGE G. STILLWELL, M.D. Pp. 843; 189 ills. Philadelphia: W. B. Saunders Co., 1955. Price, $12.50.

THE collected papers of the Mayo Clinic and Mayo Foundation have been published yearly for the past 46 years. The present volume is made up of 843 pages, containing 134 articles and spreading over every specialty. The illustrations are very good. The material contained in this volume is representative of the papers published from the Mayo Clinic from December 1, 1953, to November 30, 1954, inclusive. Of the total number of papers, 62 appear in full, 52 by abridgement, 20 by abstract, and 495 by title only. Therefore, it is easy to see that a very wide variety of subjects is briefly discussed.

This volume represents, more or less, the present opinion of Mayo Clinic personnel on such subjects as the alimentary tract, genitourinary organs, ductless glands, blood circulatory organs, skin, chest, head, trunk, extremities, brain, spinal cord, nerves, radiology,

physical medicine, and anesthesia. Very little is completely overlooked and very little is completely covered. This book would make interesting reading for any doctor, but would seem to be of especial interest to the general practitioner.

G. R.

---

THE HUMAN ADRENAL CORTEX, VOL. VIII. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., AND MARGARET P. CAMERON, M.A., A.B.L.S. Pp. 665; 227 ills. Boston: Little, Brown & Co., 1955. Price, $10.00.

THIS volume consists of the papers and the discussions provoked by each at the 8th Ciba Foundation Conference on Endocrinology. The subject matter to be considered in connection with the human adrenal cortex was extensive and led to a division of the symposium into two parts: the first, devoted mainly to histological and biochemical aspects and cortico-medullary relationships; and the second, concerned mainly with physiological and pathological aspects, and hypothalamic and pituitary relationships.

Physiologists, biochemists, pathologists, and internists as well as endocrinologists will find much of interest in these discussions.

C. Z.

---

## NEW BOOKS

*Asthma Bronchiale.* BY PROV. DOZ. DR. MED. FRANZ WYSS. Pp. 120; 52 ills. Stuttgart: Georg Thieme Verlag, 1955 (Intercontinental Medical Book Corporation, New York, Agents for U. S. and Canada). Price, $4.15.

A STUDY of the pathological physiology of bronchial asthma and of asthmatic components in a variety of lung diseases.

R. K.

---

*Cold Injury.* Transactions of the Third Conference. Edited by M. IRENE FERRER, M.D. Pp. 226; 31 ills., 3 in color. New York: Josiah Macy, Jr. Foundation, 1955. Price, $4.50.

THIS volume is a report of the third conference on cold injury which took place, appropriately enough, at Ft. Churchill, Canada, one of the coldest communities in the world. As in previous conferences the discussers are investigators in various sciences, with cold injury as a common interest.

There are sections on circulatory and metabolic factors, metabolic studies in the Eskimo, a comparative study of young Eskimo and Indian males with acclimatized white males, fat distribution and respiratory quotient, diet and survival, and on the roles of ascorbic acid and subcutaneous fat in the prevention of cold injury in man.

Although such information might appear to be of little general interest to physicians practicing in a temperate climate, the recent employment of hypothermia in cardiac surgery demonstrates how seemingly remote scientific data may suddenly prove of practical clinical value.

N. L.

---

*Die Cytologie des Bronchialsekretes.* BY DR. MED. P. HARTMANN. Pp. 112; 68 ills. Stuttgart: Georg Thieme Verlag. 1955 (Intercontinental Medical Book Corporation, New York, Agents for U. S. and Canada). Price, $5.70.

A VALUABLE and well illustrated presentation of the normal and abnormal cells to be encountered in bronchial secretion. Clinical pathologists with a knowledge of German will find this a very useful work.

R. K.

---

*The Technique and Significance of Oestrogen Determinations.* Edited by P. ECKSTEIN AND S. ZUCKERMAN. Pp. 96; 31 ills. New York: Cambridge University Press, 1955. Price, $2.50.

THIS volume is No. 3 of the Memoirs of the Society for Endocrinology (Great Britain). It consists of the proceedings of a conference held jointly by the Society for Endocrinology and the Endocrine Section of the Royal Society of Medicine, in London, on February 17, 1954. It contains the 8 papers presented at these meetings and the general discussion that followed the morning and afternoon sessions.

Of fundamental importance is the work of Diczfalusy, in which he demonstrated in human semen, by means of counter current distribution and fluorometric analysis, all three of the commonly occurring natural estrogens: estrone, estradiol and 17B-oestriol.

The closing paper by P. M. F. Biship on The Value of Estrogen Determinations to the Clinician is of general interest and places this technique in its proper clinical perspective.

B. C.

---

*Tumor-Host Studies. The Physiological and Pharmacological Action of an Iodide-trapping Substance Formed in Tumor-bearing Animals.* BY KENNETH G. SCOTT AND CHIN-TZU PENG, University of California. Pp. 30; 6 ills. and 13 figs. Berkeley and Los Angeles: University of California Press, 1955. Price, $.75.

THIS slender paper-covered volume is one of a series on the subject of tumor-host relationship. It stems from the observation that the growth of certain tumors alters the pattern of iodine metabolism in the host. The iodine pool is increased due to a decrease in urinary excretion.

UNIVERSITY OF MICHIGAN LIBRARIES

Iodide is stored in the skin, the tumor, muscle, the gastrointestinal tract and the plasma. This increased storage appears to be due to the iodide-trapping property of a substance elaborated by the tumor. The trapping phenomenon apparently inhibits tumor transplants under a critical size. It occurs to the reviewer that this phenomenon may be related to the interval in which the host does not tolerate metastatic growth. This pamphlet is of interest primarily to those working in cancer metabolism research. E. A.

---

*Malaria Control.* Bulletin of the World Health Organization. 11, 1954. Pp. 381; illustrated. Geneva: World Health Organization, 1955. Price, $3.00.

An excellent survey of the present status of malaria control in many parts of the world. Teachers as well as those engaged in public health work in endemic areas will find this report of great interest and value. R. K.

## NEW EDITIONS

*The Quantitative Analysis of Drugs.* By D. C. Garratt, B.Sc., Ph.D. (Lond.), Chief Analyst, Boots Pure Drug Co., Ltd. 2nd ed. Pp. 670; 6 ills. New York: Philosophical Library, 1955. Price, $17.50.

This volume should be useful to the drug analyst and also to those engaged in toxicological determinations. The book was formerly entitled "Drugs and Galenicals: Their Quantitative Analysis," and it has been revised by the inclusion of improved methods and of assays for some of the newer agents. Quantitative chemical methods are described in detail for the assay of various drugs. The agents and preparations included are largely those of the British Pharmacopoeia and the British Pharmaceutical Codex. Several methods are often described for individual drugs and references are given. The value of the book is increased by the author's comments and evaluations. The drugs are arranged alphabetically under their official British names. D. C.

---


## THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

*Published Monthly. Illustrated.*

*Subscription price: 1 year $10.00; 2 years $18.00.*
*(One year subscription to Canada, South and Central America, Philippines and Spain, $10.36; all other countries $11.14.)*

All foreign subscriptions payable in advance in United States dollars.

Business Correspondence: Lea & Febiger, 600 S. Washington Sq., Philadelphia 6. Pa.


## NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

Manuscripts intended for publication in The American Journal of the Medical Sciences, and correspondence should be sent to the Editor:

Dr. Richard A. Kern, Temple University School of Medicine, Philadelphia 40, Pa.

Articles are accepted for publication in The American Journal of the Medical Sciences exclusively, except in the case of subsequent publication in Society proceedings.

Manuscripts should be typewritten on one side only, of good quality paper and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle.

Each article should have a summary which gives the essential point and purpose of the paper. This summary will be translated into Interlingua for the benefit of our foreign readers.

Illustrations accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. Line drawings and charts should be prepared with black India ink. Special arrangements can be made for printing color plates, elaborate tables or an excessive number of illustrations.

References should be numbered and at the end of the articles arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

Return Postage should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

100 Reprints will be supplied gratis. Covers will be omitted on all articles. Orders of additional reprints will be supplied in multiples of 100. An order form showing cost of reprints is sent with proof. Individual reprints can usually be obtained by writing directly to the author.